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## Risk Factors for Hospitalization and Death from COVID-19 in South Sudan and Eastern Democratic Republic of the Congo

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# Risk Factors for Hospitalization and Death from COVID-19 in South Sudan and Eastern Democratic Republic of the Congo

By

Eva Leidman[1,3]*, Shannon Doocy[3]*, Grace Heymsfield[1], Abdou Sebushishe[2], Mbong Eta Ngole[2], Jennifer Majer[2], the IMC-CDC COVID-19 Research Team[4] and Iris Bollemeijer[2]

[1] US Centers for Disease Control and Prevention, Atlanta, GA

[2] International Medical Corps – US, South Sudan, DR Congo Offices

[3] Johns Hopkins Bloomberg School of Public Health, Baltimore MD, USA

[4] The study team included Deepak Kumar, Kelechi Udoh from IMC S South Sudan, Dugsiye Ahmed, Arsene Baleke, from IMC DR Congo, Jennifer Majer from IMC US, and Aimee Summers from the US CDC
*Corresponding authors

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**\*Correspondence:**
Eva Leidman, Epidemiologist, Centers for Disease Control and Prevention, 1600 Clifton Rd Atlanta, GA 30329. Email: eleidman@cdc.gov.

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Shannon Doocy, Associate Professor, Dept. of International Health, Johns Hopkins Bloomberg School of Public Health, 615 N Wolfe St, Suite E8132, Baltimore, MD, USA. Email: doocy1@jhu.edu.

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Abstract

**Objectives** To describe demographic characteristics, exposures, symptoms, and comorbidities of COVID-19 cases to evaluate risk factors of hospitalization and mortality among cases.

**Setting** Health facilities in Juba, South Sudan (SSD) (n=1) or North and South Kivu in eastern Democratic Republic of the Congo (DRC) (n=4) providing care for COVID-19 cases or referring cases for home-based care by mobile medical teams.

**Participants** All laboratory confirmed cases referred for home-based care and all cases admitted for COVID-19 treatment to study health facilities between December 2020 – June 2021. 751 individuals were eligible for enrollment. Among cases followed to discharge or death (n=519), 375 were enrolled outpatients (75.7%). A similar number of cases were followed in DRC (n=262) and South Sudan (n=257).

**Outcomes measures** Hospitalization and death

**Results** Overall mortality was 4.8% (95% CI: 3.2-6.9%); there were no outpatient deaths. Patients presenting with any symptoms had higher odds of hospitalization (AOR 2.78, 95% CI 1.47 –5.27) and all deaths occurred among symptomatic individuals. Odds of both hospitalization and mortality were greatest among cases with respiratory symptoms; presence of low oxygen levels on enrollment was strongly associated with both hospitalization (AOR 7.77, 95% CI: 4.22– 14.29) and mortality (AOR 25.29, 95% CI 6.42– 99.54). Presence of more than one chronic comorbidity was associated with 4.96 (95% CI 1.51– 16.31) times greater odds of death; neither infectious comorbidities evaluated (malaria, TB, and HIV) nor malnutrition were significantly associated with increased mortality.

**Conclusion** Older age, low oxygen level, respiratory symptoms, and chronic comorbidities were all independent risk factors for mortality in this setting; provision of equipment to measure oxygen among outpatients and development of simple triage and referral tools to refer cases with these risk factors may improve efficient use of limited inpatient resources.

**Trial registration** ClinicalTrials.gov (NCT04568499).

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**Article Summary – Strengths and Limitations**

- Sample enrolled both home-based and inpatient managed COVID-19 cases and therefore represents the spectrum of clinical severity from asymptomatic to fatal.
- Health facilities enrolling cases were in Juba, South Sudan and North and South Kivu in eastern Democratic Republic of the Congo, providing data on risk factors of severe outcomes among cases receiving care in less resources, humanitarian settings.
- The study was observational; risk factors evaluated were self-reported by cases or ascertained as part of routine care at the enrolling health facilities or by mobile health teams.
- Given barriers to case identification, including limited COVID-19 testing capacity, the cases identified for recruitment are likely a subset of all COVID-19 cases.

4

# Introduction

Characterizing risk factors for severe COVID-19 illness is critical for identifying individuals who may benefit from increased monitoring, hospitalization, or ventilator support, as well as those at increased risk of death.[1,2,3] Early identification and referral is particularly important in resource scarce contexts where access to inpatient care is limited. Risk factors for severe illness from COVID-19 with strong evidence supported by systematic reviews and meta-analyses include cancer, cerebrovascular disease, chronic kidney disease, chronic obstructive pulmonary disease, diabetes mellitus, cardiovascular disease, obesity, pregnancy, and smoking.[4,5,6,7] Demographic risk factors, including older age and male sex, have also been associated with poor prognosis.**Error! Bookmark not defined.,Error! Bookmark not defined.**

The evidence on risk factors for severe COVID-19 primarily includes case surveillance and studies conducted in higher income settings.[8] Consequently, less is known regarding how these risk factors, as well as undernutrition and exposure to infectious conditions more prevalent in lower resource settings, impact the severity of COVID-19. This evidence gap is particularly relevant given differences in the epidemiology of COVID-19 in Africa, where officially reported numbers of cases and deaths are lower than the Americas, Europe, and Asia[9] , while case fatality rates are estimated to be higher. Modeled estimates of excess mortality for patients admitted for critical care in Africa are between 11 and 23 excess deaths per 100 admissions compared with the global average mortality from COVID-19.[10] This research aimed to characterize early symptoms, exposures, comorbidities, and other risk factors associated with hospitalization and death from COVID-19 in Juba, South Sudan (SSD) and North and South Kivu, Eastern Democratic Republic of Congo (DRC) to inform identification and triage of COVID-19 cases at higher risk of mortality in resource-poor and humanitarian settings in Africa.

# Methods

An observational cohort study of COVID-19 cases enrolled between December 2020–June 2021; the last cases were discharged in July 2021 in both countries. Five study facilities operated or supported by International Medical Corps (IMC) recruited patients, including a COVID-19 treatment center in Juba, SSD and four health facilities in Eastern DRC. Study facilities in DRC included general public hospitals in Bukavu and Goma, as well as a public outpatient clinic and an NGO operated health center in Goma. Characteristics of the study facilities and care offered are described in the **Supplemental Table**. Individuals presenting for care at a study facility or referred from home-based care by mobile medical teams in the facility catchment area were eligible. Cases with a positive RT-PCR or antigen test and inpatients not tested meeting the national suspect case definitions* were eligible for enrollment. Cases were excluded from analysis if they tested negative following enrollment, were lost to follow-up (before recovery or death), or were transferred to another facility for care.

Oral consent was obtained for eligible adults and parental consent for children <18 years. Additionally, assent was obtained for children 12–17 years. Participants receiving inpatient care were followed up daily, whereas outpatients were followed up weekly through home visits and/or phone interviews. All participants were followed until COVID-19 recovery, death, or loss to follow-up. Cases treated as inpatient were considered recovered if they were discharged alive from inpatient care. Patients treated at home were considered recovered if they met one of the following conditions: resolution of fever for at least 48 hours without the use of fever-reducing medications and with improvement of other symptoms; or

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* In DRC, a case met the syndromic case definition if they had one or more of the following sign(s) or symptom(s): fever, dry cough, headache, severe fatigue, sore throat, shortness of breath, dyspnea (difficulty breathing), muscle or joint pain, or coryza (common cold). In South Sudan, suspect cases presented with acute onset of fever ≥38°C and cough, or an acute onset of any three or more signs or symptoms, including those in the DRC case definition as well as anorexia, nausea, vomiting, diarrhea, and altered mental status.

5

asymptomatic at two sequential follow-up visits. For outpatients, three attempts to contact were made before an individual was considered lost to follow-up.

Data on sociodemographic characteristics, COVID-19 exposures and symptoms, self-reported health history, anthropometric measurements, and SARS-COV-2 tests (RT-PCR and/or antigen) were collected at enrollment by research nurses using a standard data collection instrument. Anthropometric measures of MUAC, weight, height, and edema were assessed using standard procedures.[11] Malaria was evaluated using a rapid diagnostic test if ordered per the facility's standard operating procedures. Hemoglobin A1c (HbA1c) was measured using an at home test kit for individuals who reported history of diabetes. Oxygen saturation, pulse rate, and perfusion index were evaluated using the Masimo Rad 57 or Multi-parameter Patient Monitor[†][12,13] Hemoglobin concentration was evaluated using either a HemoCue 301 or Masimo Rad 57 device.[‡] Anemia and nutritional status were classified based on World Health Organization (WHO) cutoffs.[14,15,16,17] Cutoffs for other clinical conditions, including poorly controlled diabetes (HbA1c>8.0%) and low oxygen levels (<94%) were defined to align with national treatment guidelines and case definitions.

In DRC, data was recorded on paper and subsequently uploaded to CommCare, a secure online data collection platform for collecting longitudinal patient data, and in SSD, data were directly entered. Analyses were conducted using R (version 4.0.4). Distributions of continuous variables were compared by country of enrollment and hospitalization status using Kruskal-Wallis test, Fisher's exact test was used for categorical parameters. All demographic characteristics, COVID-19 exposures, symptoms, vital signs, and comorbidities evaluated as risk factors for hospitalization and mortality are presented in Table 1 and 2; parameters are presented as they were parameterized in models. Parameters were significant at p<0.1 in unadjusted models were evaluated in generalized linear mixed models (GLMM) for mortality and hospitalization; patients were considered hospitalized if ever admitted into inpatient care while enrolled in the study. Two-level GLMMs were fitted using a logit link to account for the expected correlation in outcomes within hospitals. Given the large number of risk factors of interest, separate models were built for each risk factor additionally adjusted for patient age, sex, country of enrollment, and nationality as fixed effects; results are reported as adjusted odds ratios (AOR) with 95% CIs with a p-value of <0.05 considered significant.

## Ethics Approval Statement and Funding

This study was reviewed and approved by the Johns Hopkins University Institutional Review Board (IRB number: IRB00000758), the South Sudan Ministry of Health Ethics Committee, the University of Kinshasa School of Public Health, and the US CDC. The study is registered with ClinicalTrials.gov (NCT04568499). The study was funded by USAID (award 72OFDA20GR0221). USAID had no role in the conceptualization, design, data collection, analysis, interpretation, and drafting of study findings.

## Patient and Public Involvement

Patients with COVID-19 and their families were not involved in setting the research question, outcome measures, design and implementation of the study given the emergency nature of the study. However, patients and their families were involved in dissemination of the findings at interim points throughout the study which helped to inform triage, referral, and care in the enrolling countries.

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[†] Both devices were used in DRC. The Multi-parameter Patient Monitor -YK8000K was used in South Sudan throughout the study.
[‡] Masimo devices were used at facilities in DRC between April and June 2021. The HemoCue was used between December 2020 and April 2021 in DRC and throughout the study in South Sudan.

6

**Table 1. Demographics characteristics and exposures of patients, by country and location of treatment**

| | All participants | | By Enrollment Country | | | By Location of Treatment | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | | | DR Congo, N=262 | S Sudan, N=257 | p-value | Ever Hospitalized, N=146 | Never Hospitalized, N=373 | p-value |
| | N | n (%) | n (%) | n (%) | | n (%) | n (%) | |
| **Age (years)** (Mean, SD) | 519 | 40.6 ±15.6 | 40.2 ± 17.8 | 41.1 ± 12.9 | 0.45 | 48.0 ±18.8 | 37.7 ± 13.0 | **<0.001** |
| **Age categories (years)** | 519 | | | | **<0.001** | | | **<0.001** |
| < 18 | | 21(4.0%) | 20(7.6%) | 1(0.4%) | | 5(3.4%) | 16(4.3%) | |
| 18-44 | | 308(59.3%) | 139(53.1%) | 169(65.8%) | | 58(39.7%) | 250(67.0%) | |
| 45-64 | | 147(28.3%) | 77(29.4%) | 70(27.2%) | | 51(34.9%) | 96(25.7%) | |
| 65+ | | 43(8.3%) | 26(9.9%) | 17(6.6%) | | 32(21.9%) | 11(2.9%) | |
| **Sex** | 519 | | | | **<0.001** | | | 0.27 |
| Male | | 346(66.7%) | 153(58.4%) | 193(75.1%) | | 92(63.0%) | 254(68.1%) | |
| Female | | 173(33.3%) | 109(41.6%) | 64(24.9%) | | 54(37.0%) | 119(31.9%) | |
| **Nationality** | 516 | | | | **<0.001** | | | **<0.001** |
| National (DRC/ SSD) | | 395(76.6%) | 247(94.3%) | 148(58.3%) | | 127(88.2%) | 268(72.0%) | |
| African country | | 68(13.2%) | 8(3.1%) | 60(23.6%) | | 7(4.9%) | 61(16.4%) | |
| Non-African country | | 53(10.3%) | 7(2.7%) | 46(18.1%) | | 10(6.9%) | 43(11.6%) | |
| **Study Site** | 519 | | | | | | | 0.004 |
| Juba | | 257(49.5%) | — | 257(100.0%) | | 57(39.0%) | 200(53.6%) | |
| North Kivu | | 173(33.3%) | 173(66.0%) | — | | 64(43.8%) | 109(29.2%) | |
| South Kivu | | 89(17.1%) | 89(34.0%) | — | | 25(17.1%) | 64(17.2%) | |
| **Reason for testing** | 491 | | | | **<0.001** | | | **<0.001** |
| COVID-19 symptoms | | 196(39.9%) | 127(53.4%) | 69(27.3%) | | 84(60.9%) | 112(31.7%) | |
| Known COVID exposure | | 71(14.5%) | 33(13.9%) | 38(15.0%) | | 12(8.7%) | 59(16.7%) | |
| Travel | | 211(43.0%) | 76(31.9%) | 135(53.4%) | | 40(29.0%) | 171(48.4%) | |
| Other | | 13(2.6%) | 2(0.8%) | 11(4.3%) | | 2(1.4%) | 11(3.1%) | |
| **Risk of Exposure** | | | | | | | | |
| Work outside the home | 519 | 161(31.0%) | 69(26.3%) | 92(35.8%) | **0.020** | 57(39.0%) | 104(27.9%) | **0.013** |
| Health care worker | 516 | 48(9.3%) | 29(11.1%) | 19(7.5%) | 0.15 | 8(5.6%) | 40(10.8%) | 0.068 |
| Visit to health care facility[1] | 517 | 188(36.4%) | 85(32.6%) | 103(40.2%) | 0.070 | 64(43.8%) | 124(33.4%) | **0.027** |
| Caring for COVID patient | 506 | 14(2.8%) | 6(2.4%) | 8(3.2%) | 0.58 | 3(2.1%) | 11(3.0%) | 0.77 |
| Contact with a COVID case | 262 | 80(30.5%) | 48(35.6%) | 32(25.2%) | 0.069 | 15(26.3%) | 65(31.7%) | 0.43 |

[1] As a health care worker and/or as a care provider to a family/ friend/ caregiver, within the past four weeks

**Table 2. Symptoms, comorbidities and risk factors reported at enrollment, by country and location of treatment**

| | | All patients | By Enrollment Country | | | By Location of Treatment | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | | | DR Congo, N=262 | S Sudan, N=257 | p-value | Ever Hospitalized N=146 | Never Hospitalized N=373 | p-value |
| | N | n (%) | n (%) | n (%) | | n (%) | n (%) | |
| **Primary Outcomes** | | | | | | | | |
| Ever hospitalized | 519 | 146 (28.1%) | 89 (34.0%) | 57 (22.2%) | **0.003** | -- | -- | -- |
| Died | 519 | 25 (4.8%) | 8 (3.1%) | 17 (6.6%) | 0.058 | 25 (17.1%) | 0 (0.0%) | **<0.001** |
| **Symptoms (self-reported)** | | | | | | | | |
| Symptomatic | 519 | 383(73.8%) | 243(92.7%) | 140(54.5%) | **<0.001** | 131(89.7%) | 252(67.6%) | **<0.001** |
| Cough | 519 | 272(52.4%) | 176(67.2%) | 96(37.4%) | **<0.001** | 104(71.2%) | 168(45.0%) | **<0.001** |
| Sore throat | 518 | 127(24.5%) | 54(20.7%) | 73(28.4%) | **0.041** | 52 (35.9%) | 75 (20.1%) | **<0.001** |
| Runny nose | 518 | 160 (30.9%) | 106 (40.6%) | 54 (21.0%) | **<0.001** | 54 (37.2%) | 106 (28.4%) | 0.051 |
| Shortness of breath | 519 | 96 (18.5%) | 51 (19.5%) | 45 (17.5%) | 0.57 | 76 (52.1%) | 20 (5.4%) | **<0.001** |
| Wheezing | 519 | 18 (3.5%) | 12 (4.6%) | 6 (2.3%) | 0.16 | 14 (9.6%) | 4 (1.1%) | **<0.001** |
| Chest pain | 518 | 110 (21.2%) | 63 (24.1%) | 47 (18.3%) | 0.10 | 63 (43.4%) | 47 (12.6%) | **<0.001** |
| Headache | 518 | 225 (43.4%) | 154 (59.0%) | 71 (27.6%) | **<0.001** | 77 (53.1%) | 148 (39.7%) | **0.006** |
| Muscle/ joint pain | 518 | 111 (21.4%) | 63 (24.1%) | 48 (18.7%) | 0.13 | 50 (34.5%) | 61 (16.4%) | **<0.001** |
| Fatigue/ malaise | 519 | 199 (38.3%) | 136 (51.9%) | 63 (24.5%) | **<0.001** | 88 (60.3%) | 111 (29.8%) | **<0.001** |
| Vomiting/ nausea | 519 | 41 (7.9%) | 31 (11.8%) | 10 (3.9%) | **<0.001** | 22 (15.1%) | 19 (5.1%) | **<0.001** |
| Abdominal pain | 519 | 60 (11.6%) | 35 (13.4%) | 25 (9.7%) | 0.20 | 24 (16.4%) | 36 (9.7%) | **0.030** |
| Chills | 519 | 61 (11.8%) | 42 (16.0%) | 19 (7.4%) | **0.002** | 24 (16.4%) | 37 (9.9%) | **0.038** |
| Loss of taste/ smell | 515 | 87 (16.9%) | 48 (18.6%) | 39 (15.2%) | 0.30 | 25 (17.2%) | 62 (16.8%) | 0.89 |
| Loss of appetite | 519 | 17 (3.3%) | 12 (4.6%) | 5 (1.9%) | 0.092 | 8 (5.5%) | 9 (2.4%) | 0.10 |
| **Clinical presentation** | | | | | | | | |
| Fever (>37.5C) | 518 | 68 (13.1%) | 45 (17.2%) | 23 (9.0%) | **0.006** | 20 (13.7%) | 48 (12.9%) | 0.81 |
| Hypothermia (≤35.0C) | 518 | 30 (5.8%) | 23 (8.8%) | 7 (2.7%) | 0.003 | 10 (6.8%) | 20 (5.4%) | 0.52 |
| Low oxygen level (<94%) | 481 | 91 (18.9%) | 55 (24.1%) | 36 (14.2%) | **0.006** | 64 (43.8%) | 27 (8.1%) | **<0.001** |
| **Appearance at enrollment** | 519 | | | | **<0.001** | | | **<0.001** |
| Acutely ill: non-ambulatory | | 79 (15.2%) | 49 (18.7%) | 30 (11.7%) | | 79 (54.1%) | 0 (0.0%) | |
| Acutely ill: ambulatory | | 145 (27.9%) | 133 (50.8%) | 12 (4.7%) | | 24 (16.4%) | 121 (32.4%) | |
| Healthy looking | | 295 (56.8%) | 80 (30.5%) | 215 (83.7%) | | 43 (29.5%) | 252 (67.6%) | |
| **Infectious co-morbidities** | | | | | | | | |
| Malaria[1]   Confirmed | | 7 (7.8%) | 6 (8.8%) | 1 (4.5%) | | 7 (11.5%) | 0 (0.0%) | |
| Suspected | 90 | 44 (48.9%) | 28 (41.2%) | 16 (72.7%) | **0.003** | 15 (24.6%) | 29 (100.0%) | **<0.001** |
| Negative | | 39 (43.3%) | 34 (50.0%) | 5 (22.7%) | | 39 (63.9%) | 0 (0.0%) | |
| Tuberculosis[3] | 518 | 4 (0.8%) | 1 (0.4%) | 3 (1.2%) | 0.37 | 2 (1.4%) | 2 (0.5%) | 0.32 |
| HIV[3] | 291 | 5 (1.7%) | 4 (4.0%) | 1 (0.5%) | 0.051 | 2 (2.9%) | 3 (1.3%) | 0.33 |
| Any infectious co-morbidity | 296 | 16 (5.4%) | 11 (10.5%) | 5 (2.6%) | **0.004** | 11 (15.1%) | 5 (2.2%) | **<0.001** |
| **Chronic co-morbidities** | | | | | | | | |
| Diabetes[2] | 519 | 40 (7.7%) | 20 (7.6%) | 20 (7.8%) | 0.95 | 28 (19.2%) | 12 (3.2%) | **<0.001** |
| High blood pressure (>130/80) | 508 | 163 (32.1%) | 56 (22.0%) | 107 (42.1%) | **<0.001** | 48 (33.6%) | 115 (31.5%) | 0.65 |
| Chronic cardiac disease history[2] | 514 | 18 (3.5%) | 13 (5.0%) | 5 (2.0%) | 0.059 | 12 (8.5%) | 6 (1.6%) | **<0.001** |
| Chronic pulmonary disease[2] | 518 | 9 (1.7%) | 2 (0.8%) | 7 (2.7%) | 0.10 | 2 (1.4%) | 7 (1.9%) | >0.99 |
| Current smoker[2] | 515 | 21 (4.1%) | 4 (1.5%) | 17 (6.7%) | **0.003** | 3 (2.1%) | 18 (4.8%) | 0.16 |
| Hypertension[2] | 518 | 77 (14.9%) | 39 (14.9%) | 38 (14.8%) | 0.99 | 42 (29.0%) | 35 (9.4%) | **<0.001** |
| Any chronic co-morbidity | 519 | 229 (44.1%) | 84 (32.1%) | 145 (56.4%) | **<0.001** | 78 (53.4%) | 151 (40.5%) | **0.008** |
| ≥2 chronic co-morbidities | 519 | 80 (15.4%) | 37 (14.1%) | 43 (16.7%) | 0.41 | 43 (29.5%) | 37 (9.9%) | **<0.001** |
| **Nutritional status[3]** | 470 | | | | 0.79 | | | 0.016 |
| Obese | | 84 (17.9%) | 48 (19.4%) | 36 (16.1%) | | 23 (21.5%) | 61 (16.8%) | |
| Overweight | | 166 (35.3%) | 85 (34.4%) | 81 (36.3%) | | 32 (29.9%) | 134 (36.9%) | |
| Normal weight | | 203 (43.2%) | 106 (42.9%) | 97 (43.5%) | | 43 (40.2%) | 160 (44.1%) | |
| Underweight | | 17 (3.6%) | 8 (3.2%) | 9 (4.0%) | | 9 (8.4%) | 8 (2.2%) | |
| **Anemia Status[4]** | | | | | | | | |
| Anemic | 213 | 26 (12.2%) | 19 (9.6%) | 7 (46.7%) | **<0.001** | 15 (25.0%) | 11 (7.2%) | **<0.001** |

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[1] RDTs were performed for inpatients suspected of having malaria by clinical staff; routine testing was not available. Suspected malaria refers to cases for whom no RDT was performed, who received anti-malarial medications taken prior to enrollment, and who reported chills and/or fever (measured or reported).

[2] Condition was self-reported by patient at enrollment.

[3] Obesity: in adults BMI >=30, in children up to 19 years old: BMI-for-age-z-score >3 SD.  Overweight: in adults BMI <30 and >=25, in children: BMI-for-age-z-score 2-2.99 SD. Underweight: in adults: BMI <18.5, in children <-2 SD. Children <5 (n=8) were excluded from this analysis, of them 0/7 with valid anthropometric measurements were malnourished by WHZ, and 2/7 were MAM by MUAC (>=11.5 cm & <12.5 cm).

[4] Children <12 years old: Hemoglobin < 11 g/dL, Children 12-15 years old: Hemoglobin < 12 g/dL, Non-pregnant women >=15 years old: Hemoglobin < 12 g/ dL, Pregnant women >=15 years old: Hemoglobin < 11 g/dL, Males >=15 years old: Hemoglobin <13 g/dL

9

## Results

During the study period, 751 individuals were eligible per the study protocol of which 592 (78.8%) consented to participate **(Figure 1)**. Among cases followed to discharge (n=519), 375 were enrolled as outpatients (75.7%) of which all were confirmed cases and 144 were enrolled inpatient (24.3%) of which 137 were confirmed and 7 were suspect cases. Similar numbers of cases were followed to discharge (recovery or death) in SSD (n=257) and DRC (n=262).

Patient demographics, exposure history, symptoms at enrollment, and clinical history differed by country **(Table 1)**. SSD had significantly fewer nationals (58.3% vs 94.3%, p<0.001) and female cases (24.9% vs. 41.6%, p<0.001). There was no significant difference in mean age by country, however, the proportion of individuals >65 years was slightly higher in DRC (9.9% vs 6.6%). Cases in SSD were more likely to work outside the home (35.8% vs 26.3%, p=0.020); otherwise, risk factors for exposure were similar. Cases in DRC were more likely to present with symptoms (92.7% vs 54.5%, p<0.001), likely a function of testing protocols. The majority of cases in SSD were identified by travel screening (53.4%), whereas in DRC most participants sought testing after experiencing COVID-19 like symptoms (53.4%). Overall, the most common symptoms were cough (52.4%), headache (43.4%), fatigue/malaise (38.3%), and runny nose (30.9%) **(Table 2)**.

Evaluating differences in characteristics of hospitalized patients was a primary aim given that a minority of cases (28.1%) ever received inpatient care. Participants in DRC were more likely to be hospitalized (34.0% vs 22.2%, p=0.003), likely due in part to differences in case identification by country. Hospitalized patients were older than outpatients (mean age 48.0 vs 37.7 years, p<0.001) and more likely to be a national of the country of enrollment (88.2% vs 72.0%, p<0.001). Hospitalized patients were also more likely than outpatients to have been tested due to COVID-19 like symptoms (60.9% vs 31.7%, p<0.001), and for almost all symptoms assessed, a significantly higher proportion of cases among inpatients self-reported experiencing the symptom than among outpatient (**Table 2**).

The prevalence of infectious comorbidities (i.e., malaria, tuberculosis, and/or HIV) overall was low (5.4%), however, hospitalized cases were more likely to present with one or more of the assessed infectious comorbidities (15.1% vs 2.2%, p<0.001); all confirmed malaria cases (n=7) were hospitalized. Chronic comorbidities were more prevalent, with 44.1% of persons presenting with at least one chronic comorbidity and 15.4% presenting with two or more chronic comorbidities. Chronic comorbidities were more common among hospitalized patients (53.4% vs 40.5%, p<0.008).High blood pressure was the most frequently reported chronic comorbidity, with similar prevalence between inpatients and outpatients (p=0.65). Obesity and self-reported history of hypertension, diabetes, and chronic cardiac disease all were significantly more prevalent among hospitalized cases (p<0.02 for all comparisons). Among individuals with diabetes history for whom HbA1c values were available (n=28), diabetes was poorly controlled (HbA1c>8.0%) for 32.1%; neither differences by country nor by hospitalization were significant. Anemia was also more common (25.0% vs 7.2%, p<0.001) among hospitalized cases.

Overall, the mortality proportion was 4.8% (CI: 3.2-6.9%). The mortality proportion was 17.1% (CI: 11.6-23.8%) among patients ever hospitalized; there were no outpatient deaths. All deceased individuals were symptomatic at enrollment and classified by clinical staff as acutely ill and non-ambulatory; as such, estimates are unadjusted for severity at enrollment. Mortality was higher in South Sudan (6.6%) than DRC (3.3%), and this difference was marginally significant (p=0.058). Regression models evaluated the adjusted odds ratio of hospitalization (**Table 3**) and mortality (**Table 4**). Age and nationality were the only demographic characteristics significantly associated with hospitalization and mortality. Odds of hospitalization were 12.16 (CI: 5.67 −26.09) times greater among older individuals (≥65 years) compared with individuals <45 years of age; odds of mortality were 49.75 (CI 12.23 −202.33) times greater for older

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adults. Nationals had 2.48 (CI: 1.31 −4.69) times higher odds of hospitalization and 8.90 (95% CI: 1.87 − 42.39) times higher odds of mortality than patients that were not nationals of the country of enrollment.

11

**Table 3: Unadjusted and Adjusted Odds of Hospitalization by Select Patient Characteristics**

| | Unadjusted Odds | | | Adjusted Odds[1] | | |
|---|---|---|---|---|---|---|
| | Point Estimate | 95% CI | p-value | Point Estimate | 95% CI | p-value |
| **Demographic Characteristics** | | | | | | |
| Age (ref: age<45 years) | | | | | | |
|   Age 45-64 years | 2.24 | (1.45-3.47) | **<0.001** | 2.42 | (1.53-3.83) | **<0.001** |
|   Age 65+ years | 12.28 | (6.04-26.76) | | 12.16 | (5.67-26.09) | |
| Male sex (ref: female) | 0.80 | (0.53-1.19) | 0.27 | 0.93 | (0.59-1.46) | 0.759 |
| South Sudan (ref: DRC) | 0.55 | (0.38-0.82) | **0.003** | 0.77 | (0.45-1.33) | 0.353 |
| National (ref: non-nationals) | 2.90 | (1.67-5.05) | **<0.001** | 2.48 | (1.31-4.69) | **0.005** |
| **Primary Reason for Testing** | | | | | | |
| COVID-19 like symptoms (ref: other)[2] | 3.35 | (2.22-5.04) | **<0.001** | 2.59 | (1.62-4.16) | <0.001 |
| **Clinical Presentation at Enrollment** | | | | | | |
| Low oxygen level (<94%) | 8.90 | (5.34-14.85) | **<0.001** | 7.77 | (4.22-14.29) | **<0.001** |
| **Symptoms at Enrollment (self-reported)** | | | | | | |
| Symptomatic (ref: asymptomatic) | 4.19 | (2.36-7.46) | **<0.001** | 2.78 | (1.47-5.27) | **0.002** |
| Cough | 3.02 | (2.00-4.56) | **<0.001** | 2.27 | (1.43-3.62) | **<0.001** |
| Fatigue/malaise | 3.58 | (2.40-5.34) | **<0.001** | 2.80 | (1.77-4.41) | **<0.001** |
| Shortness of breath | 19.16 | (11-33.39) | **<0.001** | 21.37 | (10.91-41.87) | **<0.001** |
| Chest pain | 5.33 | (3.4-8.35) | **<0.001** | 4.48 | (2.71-7.43) | **<0.001** |
| Wheezing | 9.78 | (3.16-30.25) | **<0.001** | 8.34 | (2.42-28.67) | **<0.001** |
| Joint pain | 2.69 | (1.74-4.17) | **<0.001** | 2.08 | (1.25-3.46) | **0.005** |
| Loss of appetite | 2.34 | (0.89-6.2) | 0.086 | 1.52 | (0.52-4.42) | 0.442 |
| Runny Nose | 1.49 | (1.00-2.24) | 0.052 | 1.43 | (0.91-2.25) | 0.117 |
| Sore Throat | 2.22 | (1.45-3.39) | **<0.001** | 2.29 | (1.43-3.68) | **<0.001** |
| Headache | 1.72 | (1.17-2.53) | **0.006** | 1.36 | (0.88-2.12) | 0.167 |
| Nausea | 3.31 | (1.73-6.31) | **<0.001** | 2.88 | (1.42-5.85) | **0.003** |
| Abdominal pain | 1.84 | (1.06-3.21) | **0.032** | 1.73 | (0.95-3.17) | 0.074 |
| Diarrhea | 2.21 | (0.93-5.24) | 0.071 | 2.44 | (0.94-6.29) | 0.065 |
| Chills | 1.79 | (1.03-3.11) | **0.040** | 1.83 | (0.91-3.7) | 0.092 |
| **Exposure** | | | | | | |
| Visit to health care facility | 1.55 | (1.05-2.3) | **0.027** | 1.41 | (0.91-2.18) | 0.121 |
| Worked outside the home | 1.66 | (1.11-2.48) | **0.014** | 2.56 | (1.61-4.06) | **<0.001** |
| Health care worker | 0.49 | (0.22-1.07) | 0.073 | 0.46 | (0.20-1.06) | 0.067 |
| **Comorbidities** | | | | | | |
| Any infectious comorbidity | 7.74 | (2.59-23.1) | **<0.001** | 4.92 | (1.46-16.62) | **0.010** |
| Diabetes | 7.14 | (3.52-14.48) | **<0.001** | 5.08 | (2.28-11.32) | **<0.001** |
| Chronic cardiac disease | 5.63 | (2.07-15.31) | **<0.001** | 3.65 | (1.21-11.04) | **0.022** |
| Hypertension | 3.94 | (2.39-6.49) | **<0.001** | 2.65 | (1.45-4.85) | **0.002** |
| Chronic comorbidities (ref: none) [3] | | | | | | |
|   One chronic comorbidity | 1.00 | (0.63-1.6) | **<0.001** | 1.19 | (0.7-2.05) | **0.002** |
|   Two or more chronic comorbidities | 3.79 | (2.27-6.39) | | 3.11 | (1.62-5.96) | |
| **Nutrition** | | | | | | |
| Body mass index[4] | | | | | | |
|   Obesity (ref: normal weight) | 1.40 | (0.78-2.52) | **0.021** | 1.00 | (0.52-1.95) | **0.013** |
|   Overweight (ref: normal weight) | 0.89 | (0.53-1.48) | | 0.70 | (0.39-1.25) | |
|   Underweight (ref: normal weight) | 4.19 | (1.52-11.78) | | 5.04 | (1.63-15.57) | |
| Anemic5 | 4.30 | (1.84-10.04) | **<0.001** | 10.69 | (3.32-34.41) | **<0.001** |

[1] Individual risk factor models adjusted for age, sex, country of enrollment and (non)national status (fixed effects) and facility (random effect)

[2] Included travel, close contact with a confirmed case, or other reason

³ Self-reported history of diabetes, chronic cardiac disease, chronic pulmonary disease, hypertension, asthma, current smoking, or a blood pressure at enrollment of >130/80.

⁴ Obesity: in adults BMI >=30, in children up to 19 years old: BMI-for-age-z-score >3 SD.  Overweight: in adults BMI <30 and >=25, in children: BMI-for-age-z-score 2-2.99 SD. Underweight: in adults: BMI <18.5, in children <-2 SD. Children <5 (n=8) were excluded from this analysis, of them 0/7 with valid anthropometric measurements were malnourished by WHZ, and 2/7 were MAM by MUAC (>=11.5 cm & <12.5 cm).

5 Children <12 years old: Hemoglobin < 11 g/dL, Children 12-15 years old: Hemoglobin < 12 g/dL, Non-pregnant women >=15 years old: Hemoglobin < 12 g/ dL, Pregnant women >=15 years old: Hemoglobin < 11 g/dL, Males >=15 years old: Hemoglobin <13 g/dL

13

**Table 4: Unadjusted and Adjusted Odds of Mortality by Select Patient Characteristics**

| | Unadjusted Odds | | | Adjusted Odds[1] | | |
|---|---|---|---|---|---|---|
| | Point Estimate | 95% CI | p-value | Point Estimate | 95% CI | p-value |
| **Demographic Characteristics** | | | | | | |
| Age (ref: age<45 years) | | | | | | |
| Age 45-64 years | 8.79 | (2.41-32.0) | **<0.001** | 11.42 | (3.06-3.06) | **<0.001** |
| Age 65+ years | 37.35 | (11.02-171.55) | | 49.75 | (12.23-202.33) | |
| Male sex (ref: female) | 1.62 | (0.63-4.13) | 0.314 | 2.11 | (0.73-6.15) | 0.171 |
| South Sudan (ref: DRC) | 2.25 | (0.95-5.31) | **0.064** | 5.79 | (0.89-37.83) | 0.067 |
| National (ref: non-nationals) | 3.68 | (0.85-15.83) | **0.080** | 8.9 | (1.87-42.39) | **0.006** |
| **COVID-19 Testing** | | | | | | |
| COVID-19 symptoms (ref: other reason)[2] | 17.58 | (4.07-75.87) | **<0.001** | 13.44 | (2.83-63.76) | **0.001** |
| **Clinical Presentation at Enrollment** | | | | | | |
| Acutely ill: non-ambulatory[3] | 191.56 | (25.43-1443.3) | **<0.001** | 164.67 | (18.87-1437.13) | **<0.001** |
| Low oxygen level (<94%) | 41.13 | (11.98-141.16) | **<0.001** | 25.29 | (6.42-99.54) | **<0.001** |
| **Symptoms at Enrollment (self-reported)** | | | | | | |
| Symptomatic (ref: asymptomatic) | | | | | | |
| Cough | 5.08 | (1.72-15.02) | **0.003** | 3.33 | (1.03-10.79) | **0.045** |
| Fatigue/malaise | 7.04 | (2.6-19.08) | **<0.001** | 7.09 | (2.26-22.25) | **<0.001** |
| Shortness of breath | 66.32 | (15.31-287.34) | **<0.001** | 36.45 | (7.69-172.87) | **<0.001** |
| Chest pain | 11.21 | (4.55-27.62) | **<0.001** | 6.37 | (2.32-17.51) | **<0.001** |
| Loss of taste/smell | 2.45 | (1.02-5.87) | **0.045** | 1.59 | (0.56-4.54) | 0.387 |
| Wheezing | 12.68 | (4.3-37.42) | **<0.001** | 11.54 | (3.04-43.83) | **<0.001** |
| Joint pain | 2.16 | (0.93-5.02) | 0.075 | 1.10 | (0.42-2.90) | 0.840 |
| Loss of appetite | 7.05 | (2.12-23.47) | **0.001** | 5.17 | (1.13-23.69) | **0.035** |
| **Exposure** | | | | | | |
| Visit to health care facility | 2.77 | (1.22-6.29) | 0.015 | 2.08 | (0.78-5.55) | 0.142 |
| **Comorbidities** | | | | | | |
| Confirmed/suspect malaria (ref: negative) | 0.33 | (0.09-1.19) | 0.090 | 0.14 | (0.02-0.91) | **0.040** |
| History of diabetes | 12.60 | (5.26-30.2) | <0.001 | 4.49 | (1.59-12.63) | **0.004** |
| History of hypertension | 7.26 | (3.17-16.61) | <0.001 | 2.82 | (1.06-7.49) | **0.037** |
| High blood pressure (>130/80) | 2.85 | (1.27-6.43) | 0.011 | 1.66 | (0.64-4.32) | 0.298 |
| Num. of chronic comorbidities (ref: none)[4] | | | | | | |
| One chronic comorbidity | 1.57 | (0.42-5.94) | <0.001 | 0.80 | (0.19-3.32) | **0.005** |
| Two or more chronic comorbidities | 14.25 | (5.36-44.87) | | 4.96 | (1.51-16.31) | |

[1] Individual risk factor models adjusted for age, sex, country of enrollment and (non)national status (fixed effects) and facility (random effect)

[2] Included travel, close contact with a confirmed case, or other reason

[3] General appearance at enrollment classified by clinical staff at enrollment

[4] Self-reported history of diabetes, chronic cardiac disease, chronic pulmonary disease, hypertension, asthma, current smoking, or a blood pressure at enrollment of >130/80.

14

Patients presenting with any symptoms had higher odds of hospitalization (AOR 2.78, CI 1.47 –5.27) and all deaths occurred among symptomatic individuals. Hospitalization and mortality AORs were significant for cough, fatigue, shortness of breath (SOB), chest pain, and wheezing. Joint pain, sore throat, and nausea were significantly associated with hospitalization but not mortality. Loss of appetite was significantly associated with mortality but not hospitalization. The magnitude of the effect was greatest for respiratory symptoms: SOB (hospitalization AOR 21.37, CI: 10.91– 41.87; mortality AOR 36.45, CI: 7.69 –172.87) and wheezing (hospitalization AOR 8.34, CI: 2.42– 28.67; mortality AOR 11.54, CI 3.04– 43.83). Consistently, presence of oxygen levels <94% at enrollment was strongly associated with both hospitalization and death (hospitalization AOR 7.77, CI: 4.22– 14.29; mortality AOR 25.29, 95% CI 6.42– 99.54). Among patients classified by research nurses as acutely ill and non-ambulatory on enrollment, all were hospitalized; this classification was the strongest risk factor for mortality (AOR 164.67, CI 18.87– 1437.13).

Infectious co-morbidities (malaria, TB, HIV) were only associated with increased hospitalization when analyzed as a single aggregated risk factor for presence of any assessed co-infectious disease. Presence of confirmed or suspected malaria was associated with a decreased odds of death (AOR 0.14, CI: 0.02– 0.91). History of diabetes and hypertension were both significantly associated with increased risk for hospitalization and death (p<0.005 for all comparisons). Presence of more than one chronic comorbidity was associated with 3.11 (CI 1.62– 5.96) times greater odds of hospitalization and 4.96 (CI 1.51– 16.31) odds of death. Underweight and anemia were significantly associated with hospitalization risk (underweight AOR 5.04, CI: 1.63-15.57; Anemia AOR 10.69, CI: 3.32-34.41) but not mortality.

## Discussion

Consistent with reports from other African settings,[18,19] among our sample of 519 COVID-19 patients in Eastern DRC and Juba, there were nearly three times as many patients enrolled as outpatients. Outpatients ultimately experienced no deaths during the study period. Case fatality reported in our observational cohort study (4.8%) was consequently closer to estimates from national case surveillance in DRC (1.9%), South Sudan (1.1%) and Africa overall (2.4%) as well as studies of outpatients from other settings (1.3%) than estimates among hospitalized cases; among patients admitted to intensive care units in Africa, case fatality has been estimated to approach 50%.[10,11,20]

Given both supply and demand barriers to facility-based treatment, WHO recommends that in cases where it is not possible to isolate all laboratory confirmed cases in a health care facility, groups with the highest risk of poor outcomes should be prioritized.[21] Our study provides information about the profile of patients receiving home-based care in resource poor African settings that can inform case management strategies.

Age and nationality of patients receiving home-based care differed significantly from those receiving inpatient care and both characteristics were significantly associated with odds of mortality, consistent with prior research; however, sex was not associated with either hospitalization or mortality. Older age has been well established as a strong predictor of severity and clinical outcomes from COVID-19[22], and as such, referral of older individuals for inpatient care is recommended in national protocols and global guidance. Differences in both hospitalization and survival by nationality, where SSD/DRC nationals faced increased risk compared to non-nationals, likely reflect differences in case identification, care seeking, as well as sociodemographic characteristics of these populations, as explored in the qualitative research that complemented this study (Majer J et al. Operational challenges and considerations for COVID-19 research in humanitarian settings: A qualitative study of a project in Eastern Democratic Republic of the Congo and South Sudan). The finding of no sex differences is in contrast with prior meta-analysis that have found men at higher risk of severe disease; however, a 2021 study of inpatients in Africa similarly

15

found no sex differences in mortality.[22,23,24] It is possible that greater differences in exposure and care seeking by gender in these settings confound the association between sex and severity.

In addition to age, current WHO guidance recommends that individuals who smoke, are obese, or have a history of cardiovascular disease, diabetes mellitus, chronic lung disease, are at greater risk for poor outcomes from COVID-19 and should be referred for inpatient care. [21] However, neither individuals who smoked, were obese, or had chronic lung disease in our study were significantly more likely to be treated inpatient, suggesting a potential opportunity to improve triage and referral. Interestingly, study subjects classified as being underweight and anemic were both more likely to be hospitalized but did not face increased risk of death, suggesting that triage by nutrition status may be occurring but that either these factors are not associated with death, or they can be effectively mitigated in the outpatient settings. Evidence regarding anemia and poor COVID-19 outcomes from prior meta-analyses is mixed.[25,26] We did not observe the 'j-shape' relationship between BMI and mortality reported in prior meta-analysis.[27] Additionally, consistent with prior literature,[28] history of hypertension was strongly associated with increased risk of both hospitalization and mortality, suggesting the need to screen for hypertension at initial patient consultation.

Triage of patients at risk of severe outcomes remains predominantly based on history of chronic conditions given the preponderance of evidence related to these conditions. While several cohort studies and case series suggest that individuals with HIV are at increased risk of severe outcomes,[1] and that tuberculosis and malaria may confer an increased risk of COVID-19 co-infection,[29,30] evidence on infectious comorbidities is more limited than that for chronic comorbidities. Given higher prevalence of these conditions in our target populations in DRC (HIV=1.2%[31], TB=0.3%[32], malaria=32.6%[33]) and South Sudan (HIV=2.5%[34], TB=0.1%[35], malaria=27.2%[33]) than in high income countries, gathering evidence on these conditions was a core aim of this study. However, our final samples of individuals with HIV (n=5), TB (n=4) and suspected (n=44) or confirmed (n=7) malaria were all small. Given these small samples, presence of infectious comorbidities was only a significant predictor of hospitalization when pooled. Malaria was significantly negatively associated with mortality, however, findings should be interpreted with caution given potential biases in case identification given universal testing was not conducted as part of the study protocol.

Patients presenting with evidence of respiratory symptoms were at greatest risk of death. Individuals with low oxygen levels and clinical assessment of non-ambulatory (generally in respiratory distress) had 25- and 164-times greater odds of mortality, respectively. These data suggest these high-risk individuals were being successfully triaged for inpatient care, potentially due to ability to measure oxygen among outpatients using pulse oximeters made available by the study. In August 2020, WHO revised guidance on home-based management to recommend use of home pulse oximetry as a safe, non-invasive tool for early identification of low oxygen levels in patients with initially mild or moderate COVID-19.[21] This approach is not yet universal practice in many low-income settings including South Sudan and DRC and this research suggests a need to advocate for their adoption and scale-up in resource-poor settings. Self-reported respiratory symptoms at admission (shortness of breath, wheezing, and chest pain) were also associated with increased odds of mortality which is indicative of the need for a standardized approach to respiratory assessment in outpatient screening. The strength of the associations between respiratory symptoms and mortality may be informative to improve patient triaged in these settings.

Our study is subject to four principal limitations. First, the study population reflects only patients with COVID-19 who interacted with the health system; given many barriers to case identification (including weak surveillance systems, limited COVID-19 testing capacity, and sub-optimal care seeking behaviors) the cases identified for recruitment are a subset of COVID-19 cases and may not be representative of all the caseload in the target population. In particular, while both countries had similar national protocols for prioritization of specimens for testing, a much larger proportion of specimens tested in South Sudan were

16

among travelers; the larger proportion of travelers, most of whom were asymptomatic or had only mild symptoms, in South Sudan than in DRC is reflected in our sample. Second, among eligible individuals, 76.7% in SSD and 15.6% in DRC could not be reached given invalid or missing phone numbers and addresses; identification and enrollment of outpatients was particularly challenging, and limitations likely resulted in further sampling bias. Thirdly, inability to rapidly scale study staff during the February/March 2021 surge and a health worker strike in SSD, and in DRC security issue, and the May 22, 2021 eruption of Mt. Nyiragongo in DRC contributed to a smaller sample than planned (n=1000), reducing power to identify other potentially significant risk factors. Finally, infectious comorbidities were self-reported, potentially resulting in under-detection; these conditions were rarely observed in the final sample and the study lacked power to adequately assess their relationship with adverse COVID-19 outcomes.

## Conclusions

Risk factors for mortality observed in our study were generally consistent with those identified in the current WHO guidance on clinical evaluation of COVID-19 patients for risk factors of severe disease based on evidence from higher income settings.[21] Individuals who were older, presenting with low oxygen levels, or reporting a history of diabetes, chronic cardiac disease, and hypertension were more likely to be hospitalized suggesting successful triage and referral of patients at increased risk of death. Individuals with evidence of respiratory distress – as reported by the patient, evaluated by clinical staff, or presenting with low oxygen – were at greatest risk of mortality. Given small samples, evaluation of individual infectious comorbidities, anemia and wasting is limited; however, pooled data suggests increased risk of hospitalization but not mortality.

The evaluation of risk factors for severe COVID-19 presented in this study may be informative for developing locally adapted tools for improving patient triage and referral, to support efforts to reduce morbidity and mortality in these settings. Similar tools to support community case managers in identifying children at greatest need for clinical management have been effective for childhood illnesses.[36] Triage and referral efforts may be most impactful where mobile medical teams are provided equipment to evaluate oxygen levels and assess symptoms of respiratory distress.

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**Figure 1. Study inclusion criteria flow chart**

[1] Of the 375 individuals enrolled outpatient, 2 individuals in South Sudan were subsequently admitted for in-patient care.
[2] Cases were confirmed by real-time reverse transcription polymerase chain reaction (RT-PCR) (90% of confirmed cases) or antigen tests (10% of confirmed cases)
[3] National case definitions were used to classify individuals as suspect cases. Of the suspect cases followed to discharge (n=7), 2 were never tested, 3 did not receive their test results, and 2 had specimens collected >3 days after enrollment.

18

**Declaration of Interest:** All authors have signed the IJCME declaration of interest forms and have no conflicts of interest to report

**Data sharing:** Deidentified data from this study are available at the Humanitarian Data Exchange.

**Author Contribution:** Conceptualization (EL, SD, JM, IB), funding acquisition (EL, SD, IB), methodology (EL, SD, JM, AS, MEN, IB), project administration (SD, IB), data collection and curation (EL, JM, GH, AS, MEN), formal analysis (EL, GH), drafting manuscript (EL, SD), critical review and editing of the manuscript (JM, GH, AS, MEN, IB), supervision (SD, IB), validation of the study (SD)

**Disclaimer**: The findings and conclusions are those of the authors and do not necessarily represent the official position of their respective institutions.

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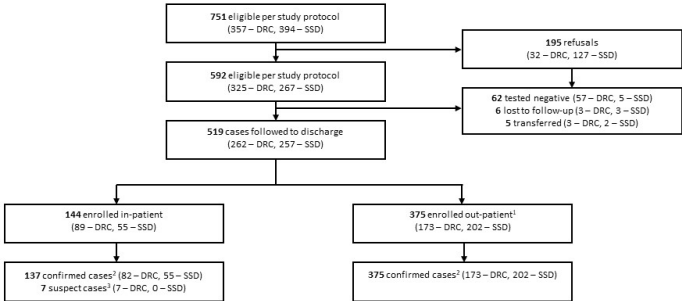49
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Figure 1. Study inclusion criteria flow chart
1 Of the 375 individuals enrolled outpatient, 2 individuals in South Sudan were subsequently admitted for in-patient care.
2 Cases were confirmed by real-time reverse transcription polymerase chain reaction (RT-PCR) (90% of confirmed cases) or antigen tests (10% of confirmed cases)
3 National case definitions were used to classify individuals as suspect cases. Of the suspect cases followed to discharge (n=7), 2 were never tested, 3 did not receive their test results, and 2 had specimens collected >3 days after enrollment.

338x190mm (96 x 96 DPI)

**Supplemental Table.** Characteristics of Health Facilities Enrolling Cases in this Study

| | Democratic Republic of the Congo | | | | South Sudan |
|---|---|---|---|---|---|
| **Hospital Location, Type and Study Enrollments** | | | | | |
| Location | Bukavu, South Kivu | Goma, North Kivu | Goma, North Kivu | Goma, North Kivu | Juba, Central Equatoria |
| Sector | Public | Public | Public | NGO operated | NGO operated |
| Study participants enrolled as inpatients | 25 | 0 | 42 | 22 | 55 |
| Study participants referred for home based care from facility catchment area | 64 | | 109[1] | | 202 |
| **Hospital Capacity** | | | | | |
| Doctors | 86 | 0 | 36 | 42 | 9 |
| Nurses | 168 | 7 | 92 | 86 | 33 |
| COVID care beds / Total beds[2] | 22/380 | NA | 20 / 220 | 28/220 | 82/82 |
| Clinical staff trained[3] | No | No | Yes | Yes | Yes |

[1] Study participants referred for home based care from throughout Goma, North Kivu. [2]The SSD facility was a COVID-19 only referral hospital and one of the Goma DRC facilities was an outpatient only facility; [3] Staff considered trained if they received information on COVID-19 case management and infection prevention and control (IPC) for COVID-19 prior to study initiation

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## Risk Factors for Hospitalization and Death from COVID-19:
## A Prospective Cohort Study in South Sudan and Eastern
## Democratic Republic of the Congo

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# Risk Factors for Hospitalization and Death from COVID-19: A Prospective Cohort Study in South Sudan and Eastern Democratic Republic of the Congo

By

Eva Leidman[1,3]*, Shannon Doocy[3]*, Grace Heymsfield[1], Abdou Sebushishe[2], Eta Ngole Mbong [2], Jennifer Majer[2], the IMC-CDC COVID-19 Research Team[4] and Iris Bollemeijer[2]

[1] US Centers for Disease Control and Prevention, Atlanta, GA

[2] International Medical Corps – US, South Sudan, DR Congo Offices

[3] Johns Hopkins Bloomberg School of Public Health, Baltimore MD, USA

[4] The study team included Deepak Kumar, Kelechi Udoh from IMC S South Sudan, Dugsiye Ahmed, Arsene Baleke, from IMC DR Congo, Jennifer Majer from IMC US, and Aimee Summers from the US CDC

*Corresponding authors

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**\*Correspondence:**

Eva Leidman, Epidemiologist, Centers for Disease Control and Prevention, 1600 Clifton Rd Atlanta, GA 30329. Email: eleidman@cdc.gov.

Shannon Doocy, Associate Professor, Dept. of International Health, Johns Hopkins Bloomberg School of Public Health, 615 N Wolfe St, Suite E8132, Baltimore, MD, USA. Email: doocy1@jhu.edu.

2

# Abstract

**Objectives**: Our study described demographic characteristics, exposures, and symptoms, and comorbidities to evaluate risk factors of hospitalization and mortality among cases in Juba, South Sudan (SSD) and North and South Kivu in eastern Democratic Republic of the Congo (DRC).

**Design** Prospective observational cohort of COVID-19 cases

**Methods** Individuals presenting for care at one of five study facilities in SSD (n=1) or DRC (n=4) or referred from home-based care by mobile medical teams between December 2020– June 2021 were eligible for enrollment. Demographic characteristics, COVID-19 exposures, symptoms at presentation, as well as acute and chronic comorbidities were evaluated using a standard questionnaire at enrollment. Disease progression was characterized by location of care using mixed-effects regression models.

**Results** 751 individuals were eligible for enrollment. Among cases followed to discharge or death (n=519), 375 were enrolled outpatients (75.7%). A similar number of cases were enrolled in DRC (n=262) and South Sudan (n=257). Overall mortality was 4.8% (95% CI: 3.2-6.9%); there were no outpatient deaths. Patients presenting with any symptoms had higher odds of hospitalization [adjusted odds ratio (AOR) 2.78, 95% CI 1.47 −5.27] and all deaths occurred among symptomatic individuals. Odds of both hospitalization and mortality were greatest among cases with respiratory symptoms; presence of low oxygen levels on enrollment was strongly associated with both hospitalization (AOR 7.77, 95% CI: 4.22− 14.29) and mortality (AOR 25.29, 95% CI 6.42− 99.54). Presence of more than one chronic comorbidity was associated with 4.96 (95% CI 1.51− 16.31) times greater odds of death; neither infectious comorbidities evaluated, nor malnutrition, were significantly associated with increased mortality.

**Conclusions** Consistent with prior literature, older age, low oxygen level, other respiratory symptoms, and chronic comorbidities were all risk factors for mortality. Patients presenting with these characteristics were more likely to be hospitalized, providing evidence of effective triage and referral.

## Strengths and limitations of this study

- A prospective observational cohort study enrolled COVID-19 cases of all severity in South Sudan and the Democratic Republic of Congo to better characterize risk factors of hospitalization and death.
- Overall mortality was 4.8%; all patients who died were symptomatic at enrollment and there were no outpatient deaths.
- Older age, low oxygen level, other respiratory symptoms, and chronic comorbidities were all risk factors for mortality.
- Odds of both hospitalization and mortality were greatest among cases with respiratory symptoms; cases with low oxygen levels at enrollment were 25 times more likely to die, highlighting the potential benefit of measurement of oxygen during initial triage of all patients.

## Introduction

Characterizing risk factors for severe Coronavirus disease (COVID-19) is critical for identifying individuals who may benefit from increased monitoring, hospitalization, or ventilator support, as well as those at increased risk of death.[1,2,3] Early identification and referral is particularly important in resource scarce contexts where access to inpatient care is limited. Risk factors for severe illness from COVID-19 with strong evidence supported by systematic reviews and meta-analyses include cancer, cerebrovascular disease, chronic kidney disease, chronic obstructive pulmonary disease, diabetes mellitus, cardiovascular disease, obesity, pregnancy, and smoking.[4,5,6,7] Demographic risk factors, including older age and male sex, have also been associated with poor prognosis.[1,2]

The evidence on risk factors for severe COVID-19 primarily includes case surveillance and studies conducted in higher income settings.[8] Consequently, less is known regarding how these risk factors, as well as undernutrition and exposure to infectious conditions more prevalent in lower resource settings, impact the severity of COVID-19. This evidence gap is particularly relevant given differences in the epidemiology of COVID-19 in Africa, where officially reported numbers of cases and deaths are lower than the Americas, Europe, and Asia[9] , while case fatality rates are estimated to be higher. Modeled estimates of excess mortality for patients admitted for critical care in Africa are between 11 and 23 excess deaths per 100 admissions compared with the global average mortality from COVID-19.[10] This research aimed to characterize early symptoms, exposures, comorbidities, and other risk factors associated with hospitalization and death from COVID-19 in Juba, South Sudan (SSD) and North and South Kivu, Eastern Democratic Republic of Congo (DRC) to inform identification and triage of COVID-19 cases at higher risk of mortality in resource-poor and humanitarian settings in Africa.

## Methods

An observational cohort study of COVID-19 cases enrolled between December 2020–June 2021; the last cases were discharged in July 2021 in both countries. Five study facilities operated or supported by International Medical Corps (IMC) recruited patients, including a COVID-19 treatment center in Juba, SSD and four health facilities in Eastern DRC. Study facilities in DRC included general public hospitals in Bukavu and Goma, as well as a public outpatient clinic and an NGO operated health center in Goma. Characteristics of the study facilities and care offered are described in the **Supplemental Table**. Availability of therapies for inpatients are presented by facility in a companion manuscript from this study focused on inpatient management.[11] Available therapies for outpatients were limited. Individuals presenting for care at a study facility or referred from home-based care by mobile medical teams in the facility catchment area were eligible. Cases with a positive real-time reverse transcription polymerase chain reaction (RT-PCR) or antigen test and inpatients not tested meeting the national suspect case definitions[*] were eligible for enrollment. Cases were excluded from analysis if they tested negative following enrollment, were lost to follow-up (before recovery or death), or were transferred to another facility for care.

Oral consent was obtained for eligible adults and parental consent for children <18 years. Additionally, assent was obtained for children 12–17 years. Participants receiving inpatient care were followed up daily, whereas outpatients were followed up weekly through home visits and/or phone interviews. All participants were followed until COVID-19 recovery, death, or loss to follow-up. Inpatients were follow-up daily whereas outpatient cases were followed weekly. Cases treated as inpatient were considered

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[*] In DRC, a case met the syndromic case definition if they had one or more of the following sign(s) or symptom(s): fever, dry cough, headache, severe fatigue, sore throat, shortness of breath, dyspnea (difficulty breathing), muscle or joint pain, or coryza (common cold). In South Sudan, suspect cases presented with acute onset of fever ≥38°C and cough, or an acute onset of any three or more signs or symptoms, including those in the DRC case definition as well as anorexia, nausea, vomiting, diarrhea, and altered mental status.

5

recovered if they were discharged alive from inpatient care. Patients treated at home were considered recovered if they met one of the following conditions: resolution of fever for at least 48 hours without the use of fever-reducing medications and with improvement of other symptoms; or asymptomatic at two sequential follow-up visits. For outpatients, three attempts to contact were made before an individual was considered lost to follow-up.

Data on sociodemographic characteristics, COVID-19 exposures and symptoms, self-reported health history, anthropometric measurements, and SARS-COV-2 tests (RT-PCR and/or antigen) were collected at enrollment by research nurses using a standard data collection instrument. Anthropometric measures of mid-upper arm circumference (MUAC), weight, height, and edema were assessed using standard procedures.[12] Malaria was evaluated using a rapid diagnostic test if ordered per the facility's standard operating procedures. Other infectious diseases – human immunodeficiency virus (HIV) and Tuberculosis (TB) – were self-reported. Hemoglobin A1c (HbA1c) was measured using an at home test kit for individuals who reported history of diabetes. Oxygen saturation, pulse rate, and perfusion index were evaluated using the Masimo Rad 57 or Multi-parameter Patient Monitor[†][13,14] Hemoglobin concentration was evaluated using either a HemoCue 301 or Masimo Rad 57 device.[‡] Anemia and nutritional status were classified based on World Health Organization (WHO) cutoffs.[15,16,17,18] Cutoffs for other clinical conditions, including poorly controlled diabetes (HbA1c>8.0%) and low oxygen levels (<94%) were defined to align with national treatment guidelines and case definitions.

In DRC, data was recorded on paper and subsequently uploaded to CommCare, a secure online data collection platform for collecting longitudinal patient data, and in SSD, data were directly entered. Analyses were conducted using R (version 4.0.4). Distributions of continuous variables were compared by country of enrollment and hospitalization status using Kruskal-Wallis test, Fisher's exact test was used for categorical parameters. All demographic characteristics, COVID-19 exposures, symptoms, vital signs, and comorbidities evaluated as risk factors for hospitalization and mortality are presented in Table 1 and 2; parameters are presented as they were parameterized in models. Parameters were significant at p<0.1 in unadjusted models were evaluated in generalized linear mixed models (GLMM) for mortality and hospitalization; patients were considered hospitalized if ever admitted into inpatient care while enrolled in the study. Two-level GLMMs were fitted using a logit link to account for the expected correlation in outcomes within health facilities which may be observed given differences in access to medication, staffing, or quality of care available at each facility. Given the large number of risk factors of interest, separate models were built for each risk factor additionally adjusted for patient age, sex, country of enrollment, and nationality as fixed effects; results are reported as adjusted odds ratios (AOR) with 95% CIs with a p-value of <0.05 considered significant.

This study was reviewed and approved by the Johns Hopkins University Institutional Review Board, the South Sudan Ministry of Health Ethics Committee, the University of Kinshasa School of Public Health , and the US CDC. The study is registered with ClinicalTrials.gov (NCT04568499). The study was funded by USAID (award 72OFDA20GR0221). USAID had no role in the conceptualization, design, data collection, analysis, interpretation, and drafting of study findings.

## Patient and Public Involvement

Patients with COVID-19 and their families were not involved in setting the research question, outcome measures, design and implementation of the study given the emergency nature of the study. However,

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[†] Both devices were used in DRC. The Multi-parameter Patient Monitor -YK8000K was used in South Sudan throughout the study.

[‡] Masimo devices were used at facilities in DRC between April and June 2021. The HemoCue was used between December 2020 and April 2021 in DRC and throughout the study in South Sudan.

6

patients and their families were involved in dissemination of the findings at interim points throughout the study which helped to inform triage, referral, and care in the enrolling countries.

## Results

During the study period, 751 individuals were eligible per the study protocol of which 592 (78.8%) consented to participate **(Figure 1)**. Among cases followed to discharge (n=519), 375 were enrolled as outpatients (75.7%) of which all were confirmed cases and 144 were enrolled inpatient (24.3%) of which 137 were confirmed and 7 were suspect cases. Similar numbers of cases were followed to discharge (recovery or death) in SSD (n=257) and DRC (n=262). Patients were followed up for an average of 8.9 days for a total of 4,630 days of follow-up time.

Patient demographics, exposure history, symptoms at enrollment, and clinical history differed by country **(Table 1)**. SSD had significantly fewer nationals (58.3% vs 94.3%, p<0.001) and female cases (24.9% vs. 41.6%, p<0.001). There was no significant difference in mean age by country, however, the proportion of individuals >65 years was slightly higher in DRC (9.9% vs 6.6%). Cases in SSD were more likely to work outside the home (35.8% vs 26.3%, p=0.020); otherwise, risk factors for exposure were similar. Cases in DRC were more likely to present with symptoms (92.7% vs 54.5%, p<0.001), likely a function of testing protocols. The majority of cases in SSD were identified by travel screening (53.4%), whereas in DRC most participants sought testing after experiencing COVID-19 like symptoms (53.4%). Overall, the most common symptoms were cough (52.4%), headache (43.4%), fatigue/malaise (38.3%), and runny nose (30.9%) **(Table 2)**.

Evaluating differences in characteristics of hospitalized patients was a primary aim given that a minority of cases (28.1%) ever received inpatient care. Participants in DRC were more likely to be hospitalized (34.0% vs 22.2%, p=0.003), likely due in part to differences in case identification by country. Hospitalized patients were older than outpatients (mean age 48.0 vs 37.7 years, p<0.001) and more likely to be a national of the country of enrollment (88.2% vs 72.0%, p<0.001). Hospitalized patients were also more likely than outpatients to have been tested due to COVID-19 like symptoms (60.9% vs 31.7%, p<0.001), and for almost all symptoms assessed, a significantly higher proportion of cases among inpatients self-reported experiencing the symptom than among outpatient (**Table 2**).

The prevalence of infectious comorbidities (i.e., malaria, tuberculosis, and/or HIV) overall was low (5.4%), however, hospitalized cases were more likely to present with one or more of the assessed infectious comorbidities (15.1% vs 2.2%, p<0.001); all confirmed malaria cases (n=7) were hospitalized. Chronic comorbidities were more prevalent, with 44.1% of persons presenting with at least one chronic comorbidity and 15.4% presenting with two or more chronic comorbidities. Chronic comorbidities were more common among hospitalized patients (53.4% vs 40.5%, p<0.008).High blood pressure was the most frequently reported chronic comorbidity, with similar prevalence between inpatients and outpatients (p=0.65). Obesity and self-reported history of hypertension, diabetes, and chronic cardiac disease all were significantly more prevalent among hospitalized cases (p<0.02 for all comparisons). Among individuals with diabetes history for whom HbA1c values were available (n=28), diabetes was poorly controlled (HbA1c>8.0%) for 32.1%; neither differences by country nor by hospitalization were significant. Anemia was also more common (25.0% vs 7.2%, p<0.001) among hospitalized cases.

Overall, the mortality proportion was 4.8% (CI: 3.2-6.9%). The mortality proportion was 17.1% (CI: 11.6-23.8%) among patients ever hospitalized; there were no outpatient deaths. All deceased individuals were symptomatic at enrollment and classified by clinical staff as acutely ill and non-ambulatory; as such, estimates are unadjusted for severity at enrollment. Mortality was higher in South Sudan (6.6%) than DRC (3.3%), and this difference was marginally significant (p=0.058). Regression models evaluated the adjusted

7

odds ratio of hospitalization (**Table 3**) and mortality (**Table 4**). Age and nationality were the only demographic characteristics significantly associated with hospitalization and mortality. Odds of hospitalization were 12.16 (CI: 5.67 –26.09) times greater among older individuals (≥65 years) compared with individuals <45 years of age; odds of mortality were 49.75 (CI 12.23 –202.33) times greater for older adults. Nationals had 2.48 (CI: 1.31 –4.69) times higher odds of hospitalization and 8.90 (95% CI: 1.87 – 42.39) times higher odds of mortality than patients that were not nationals of the country of enrollment.

Patients presenting with any symptoms had higher odds of hospitalization (AOR 2.78, CI 1.47 –5.27) and all deaths occurred among symptomatic individuals. Hospitalization and mortality AORs were significant for cough, fatigue, shortness of breath (SOB), chest pain, and wheezing. Joint pain, sore throat, and nausea were significantly associated with hospitalization but not mortality. Loss of appetite was significantly associated with mortality but not hospitalization. The magnitude of the effect was greatest for respiratory symptoms: SOB (hospitalization AOR 21.37, CI: 10.91– 41.87; mortality AOR 36.45, CI: 7.69 –172.87) and wheezing (hospitalization AOR 8.34, CI: 2.42– 28.67; mortality AOR 11.54, CI 3.04– 43.83). Consistently, presence of oxygen levels <94% at enrollment was strongly associated with both hospitalization and death (hospitalization AOR 7.77, CI: 4.22– 14.29; mortality AOR 25.29, 95% CI 6.42– 99.54). Among patients classified by research nurses as acutely ill and non-ambulatory on enrollment, all were hospitalized; this classification was the strongest risk factor for mortality (AOR 164.67, CI 18.87– 1437.13).

Infectious co-morbidities (malaria, TB, HIV) were only associated with increased hospitalization when analyzed as a single aggregated risk factor for presence of any assessed co-infectious disease. Presence of confirmed or suspected malaria was associated with a decreased odds of death (AOR 0.14, CI: 0.02– 0.91). History of diabetes and hypertension were both significantly associated with increased risk for hospitalization and death (p<0.005 for all comparisons). Presence of more than one chronic comorbidity was associated with 3.11 (CI 1.62– 5.96) times greater odds of hospitalization and 4.96 (CI 1.51– 16.31) odds of death. Underweight and anemia were significantly associated with hospitalization risk (underweight AOR 5.04, CI: 1.63-15.57; Anemia AOR 10.69, CI: 3.32-34.41) but not mortality.

## Discussion

Consistent with reports from other African settings,[19,20] among our sample of 519 COVID-19 patients in Eastern DRC and Juba, there were nearly three times as many patients enrolled as outpatients. Outpatients ultimately experienced no deaths during the study period. Case fatality reported in our observational cohort study (4.8%) was consequently closer to estimates from national case surveillance in DRC (1.9%), South Sudan (1.1%) and Africa overall (2.4%) as well as studies of outpatients from other settings (1.3%) than estimates among hospitalized cases; among patients admitted to intensive care units in Africa, case fatality has been estimated to approach 50%.[10,21]

Given both supply and demand barriers to facility-based treatment, WHO recommends that in cases where it is not possible to isolate all laboratory confirmed cases in a health care facility, groups with the highest risk of poor outcomes should be prioritized.[22] Our study provides information about the profile of patients receiving home-based care in resource poor African settings that can inform case management strategies.

Age and nationality of patients receiving home-based care differed significantly from those receiving inpatient care and both characteristics were significantly associated with odds of mortality, consistent with prior research; however, sex was not associated with either hospitalization or mortality. Older age has been well established as a strong predictor of severity and clinical outcomes from COVID-19[23], and as such, referral of older individuals for inpatient care is recommended in national protocols and global guidance. Differences in both hospitalization and survival by nationality, where SSD/DRC nationals faced

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increased risk compared to non-nationals, likely reflect differences in case identification, care seeking, as well as sociodemographic characteristics of these populations, as explored in the qualitative research that complemented this study.[11] The finding of no sex differences is in contrast with prior meta-analysis that have found men at higher risk of severe disease; however, a 2021 study of inpatients in Africa similarly found no sex differences in mortality.[23,24,25] It is possible that greater differences in exposure and care seeking by gender in these settings confound the association between sex and severity.

In addition to age, current WHO guidance recommends that individuals who smoke, are obese, or have a history of cardiovascular disease, diabetes mellitus, chronic lung disease, are at greater risk for poor outcomes from COVID-19 and should be referred for inpatient care. [22] However, neither individuals who smoked, were obese, or had chronic lung disease in our study were significantly more likely to be treated inpatient, suggesting a potential opportunity to improve triage and referral. Interestingly, study subjects classified as being underweight and anemic were both more likely to be hospitalized but did not face increased risk of death. However, anthropometric measurements frequently could not be collected for patients who were non-ambulatory at admission; the association between availability of anthropometric measurements and clinical severity of COVID-19 at admission maybe confounding this effect. Evidence regarding anemia and poor COVID-19 outcomes from prior meta-analyses is mixed.[26,27] We did not observe the 'j-shape' relationship between body mass index (BMI) and mortality reported in prior meta-analysis.[28] Additionally, consistent with prior literature,[29] history of hypertension was strongly associated with increased risk of both hospitalization and mortality, suggesting the need to screen for hypertension at initial patient consultation.

Triage of patients at risk of severe outcomes remains predominantly based on history of chronic conditions given the preponderance of evidence related to these conditions. While several cohort studies and case series suggest that individuals with HIV are at increased risk of severe outcomes,[1] and that tuberculosis and malaria may confer an increased risk of COVID-19 co-infection,[30,31] evidence on infectious comorbidities is more limited than that for chronic comorbidities. Given higher prevalence of these conditions in our target populations in DRC (HIV=1.2%[32], TB=0.3%[33], malaria=32.6%[34]) and South Sudan (HIV=2.5%[35], TB=0.1%[36], malaria=27.2%[34]) than in high income countries, gathering evidence on these conditions was a core aim of this study. However, our final samples of individuals with HIV (n=5), TB (n=4) and suspected (n=44) or confirmed (n=7) malaria were all small. Given these small samples, presence of infectious comorbidities was only a significant predictor of hospitalization when pooled. Malaria was significantly negatively associated with mortality, however, findings should be interpreted with caution given potential biases in case identification given universal testing was not conducted as part of the study protocol.

Patients presenting with evidence of respiratory symptoms were at greatest risk of death. Individuals with low oxygen levels and clinical assessment of non-ambulatory (generally in respiratory distress) had 25- and 164-times greater odds of mortality, respectively. These data suggest these high-risk individuals were being successfully triaged for inpatient care, potentially due to ability to measure oxygen among outpatients using pulse oximeters made available by the study. In August 2020, WHO revised guidance on home-based management to recommend use of home pulse oximetry as a safe, non-invasive tool for early identification of low oxygen levels in patients with initially mild or moderate COVID-19.[22] This approach is not yet universal practice in many low-income settings including South Sudan and DRC and this research suggests a need to advocate for their adoption and scale-up in resource-poor settings. Self-reported respiratory symptoms at admission (shortness of breath, wheezing, and chest pain) were also associated with increased odds of mortality which is indicative of the need for a standardized approach to respiratory assessment in outpatient screening. The strength of the associations between respiratory symptoms and mortality may be informative to improve patient triaged in these settings.

Our study is subject to five principal limitations. First, the study population reflects only patients with COVID-19 who interacted with the health system; given many barriers to case identification (including weak surveillance systems, limited COVID-19 testing capacity, and sub-optimal care seeking behaviors) the cases identified for recruitment are a subset of COVID-19 cases and may not be representative of all the caseload in the target population.[37] In particular, while both countries had similar national protocols for prioritization of specimens for testing, a much larger proportion of specimens tested in South Sudan were among travelers; the larger proportion of travelers, most of whom were asymptomatic or had only mild symptoms, in South Sudan than in DRC is reflected in our sample. Second, among eligible individuals, 76.7% in SSD and 15.6% in DRC could not be reached given invalid or missing phone numbers and addresses; identification and enrollment of outpatients was particularly challenging, and limitations likely resulted in further sampling bias. Thirdly, inability to rapidly scale study staff during the February/March 2021 surge and a health worker strike in SSD, and in DRC security issue, and the May 22, 2021 eruption of Mt. Nyiragongo in DRC contributed to a smaller sample than planned (n=1000), reducing power to identify other potentially significant risk factors. Fourth, infectious comorbidities were self-reported, potentially resulting in under-detection; these conditions were rarely observed in the final sample and the study lacked power to adequately assess their relationship with adverse COVID-19 outcomes. Finally, to ensure rigorous supervision the study sites were all operated or supported by IMC and may therefore be better resourced than other health facilities in the two countries.

## Conclusions

Risk factors for mortality observed in our study were generally consistent with those identified in the current WHO guidance on clinical evaluation of COVID-19 patients for risk factors of severe disease based on evidence from higher income settings.[22] Individuals who were older, presenting with low oxygen levels, or reporting a history of diabetes, chronic cardiac disease, and hypertension were more likely to be hospitalized suggesting successful triage and referral of patients at increased risk of death. Individuals with evidence of respiratory distress – as reported by the patient, evaluated by clinical staff, or presenting with low oxygen – were at greatest risk of mortality. Given small samples, evaluation of individual infectious comorbidities, anemia and wasting is limited; however, pooled data suggests increased risk of hospitalization but not mortality.

The evaluation of risk factors for severe COVID-19 presented in this study may be informative for developing locally adapted tools for improving patient triage and referral, to support efforts to reduce morbidity and mortality in these settings. Similar tools to support community case managers in identifying children at greatest need for clinical management have been effective for childhood illnesses.[38] Triage and referral efforts may be most impactful where mobile medical teams are provided equipment to evaluate oxygen levels and assess symptoms of respiratory distress.

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**Table 1. Demographics characteristics and exposures of patients, by country and location of treatment**

| | | All participants | By Enrollment Country | | | By Location of Treatment | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | | | DR Congo, N=262 | S Sudan, N=257 | p-value | Ever Hospitalized, N=146 | Never Hospitalized, N=373 | p-value |
| | N | n (%) | n (%) | n (%) | | n (%) | n (%) | |
| **Age (years)** (Mean, SD) | 519 | 40.6 ±15.6 | 40.2 ± 17.8 | 41.1 ± 12.9 | 0.45 | 48.0 ±18.8 | 37.7 ± 13.0 | **<0.001** |
| **Age categories (years)** | 519 | | | | **<0.001** | | | **<0.001** |
| < 18 | | 21(4.0%) | 20(7.6%) | 1(0.4%) | | 5(3.4%) | 16(4.3%) | |
| 18-44 | | 308(59.3%) | 139(53.1%) | 169(65.8%) | | 58(39.7%) | 250(67.0%) | |
| 45-64 | | 147(28.3%) | 77(29.4%) | 70(27.2%) | | 51(34.9%) | 96(25.7%) | |
| 65+ | | 43(8.3%) | 26(9.9%) | 17(6.6%) | | 32(21.9%) | 11(2.9%) | |
| **Sex** | 519 | | | | **<0.001** | | | 0.27 |
| Male | | 346(66.7%) | 153(58.4%) | 193(75.1%) | | 92(63.0%) | 254(68.1%) | |
| Female | | 173(33.3%) | 109(41.6%) | 64(24.9%) | | 54(37.0%) | 119(31.9%) | |
| **Nationality** | 516 | | | | **<0.001** | | | **<0.001** |
| National (DRC/ SSD) | | 395(76.6%) | 247(94.3%) | 148(58.3%) | | 127(88.2%) | 268(72.0%) | |
| African country | | 68(13.2%) | 8(3.1%) | 60(23.6%) | | 7(4.9%) | 61(16.4%) | |
| Non-African country | | 53(10.3%) | 7(2.7%) | 46(18.1%) | | 10(6.9%) | 43(11.6%) | |
| **Study Site** | 519 | | | | | | | **0.004** |
| Juba | | 257(49.5%) | — | 257(100.0%) | | 57(39.0%) | 200(53.6%) | |
| North Kivu | | 173(33.3%) | 173(66.0%) | — | | 64(43.8%) | 109(29.2%) | |
| South Kivu | | 89(17.1%) | 89(34.0%) | — | | 25(17.1%) | 64(17.2%) | |
| **Reason for testing** | 491 | | | | **<0.001** | | | **<0.001** |
| COVID-19 symptoms | | 196(39.9%) | 127(53.4%) | 69(27.3%) | | 84(60.9%) | 112(31.7%) | |
| Known COVID exposure | | 71(14.5%) | 33(13.9%) | 38(15.0%) | | 12(8.7%) | 59(16.7%) | |
| Travel | | 211(43.0%) | 76(31.9%) | 135(53.4%) | | 40(29.0%) | 171(48.4%) | |
| Other | | 13(2.6%) | 2(0.8%) | 11(4.3%) | | 2(1.4%) | 11(3.1%) | |
| **Risk of Exposure** | | | | | | | | |
| Work outside the home | 519 | 161(31.0%) | 69(26.3%) | 92(35.8%) | **0.02** | 57(39.0%) | 104(27.9%) | **0.01** |
| Health care worker | 516 | 48(9.3%) | 29(11.1%) | 19(7.5%) | 0.15 | 8(5.6%) | 40(10.8%) | 0.07 |
| Visit to health care facility[1] | 517 | 188(36.4%) | 85(32.6%) | 103(40.2%) | 0.07 | 64(43.8%) | 124(33.4%) | **0.03** |
| Caring for COVID patient | 506 | 14(2.8%) | 6(2.4%) | 8(3.2%) | 0.58 | 3(2.1%) | 11(3.0%) | 0.77 |
| Contact with a COVID case | 262 | 80(30.5%) | 48(35.6%) | 32(25.2%) | 0.07 | 15(26.3%) | 65(31.7%) | 0.43 |

[1] As a health care worker and/or as a care provider to a family/ friend/ caregiver, within the past four weeks

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**Table 2. Symptoms, comorbidities and risk factors reported at enrollment, by country and location of treatment**

| | | All patients | By Enrollment Country | | | By Location of Treatment | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | | | DR Congo, N=262 | S Sudan, N=257 | p-value | Ever Hospitalized N=146 | Never Hospitalized N=373 | p-value |
| | N | n (%) | n (%) | n (%) | | n (%) | n (%) | |
| **Primary Outcomes** | | | | | | | | |
| Ever hospitalized | 519 | 146 (28.1%) | 89 (34.0%) | 57 (22.2%) | **0.003** | -- | -- | -- |
| Died | 519 | 25 (4.8%) | 8 (3.1%) | 17 (6.6%) | 0.06 | 25 (17.1%) | 0 (0.0%) | **<0.001** |
| **Symptoms (self-reported)** | | | | | | | | |
| Symptomatic | 519 | 383 (73.8%) | 243 (92.7%) | 140 (54.5%) | **<0.001** | 131 (89.7%) | 252 (67.6%) | **<0.001** |
| Cough | 519 | 272 (52.4%) | 176 (67.2%) | 96 (37.4%) | **<0.001** | 104 (71.2%) | 168 (45.0%) | **<0.001** |
| Sore throat | 518 | 127 (24.5%) | 54 (20.7%) | 73 (28.4%) | **0.04** | 52 (35.9%) | 75 (20.1%) | **<0.001** |
| Runny nose | 518 | 160 (30.9%) | 106 (40.6%) | 54 (21.0%) | **<0.001** | 54 (37.2%) | 106 (28.4%) | 0.05 |
| Shortness of breath | 519 | 96 (18.5%) | 51 (19.5%) | 45 (17.5%) | 0.57 | 76 (52.1%) | 20 (5.4%) | **<0.001** |
| Wheezing | 519 | 18 (3.5%) | 12 (4.6%) | 6 (2.3%) | 0.16 | 14 (9.6%) | 4 (1.1%) | **<0.001** |
| Chest pain | 518 | 110 (21.2%) | 63 (24.1%) | 47 (18.3%) | 0.10 | 63 (43.4%) | 47 (12.6%) | **<0.001** |
| Headache | 518 | 225 (43.4%) | 154 (59.0%) | 71 (27.6%) | **<0.001** | 77 (53.1%) | 148 (39.7%) | **0.006** |
| Muscle/ joint pain | 518 | 111 (21.4%) | 63 (24.1%) | 48 (18.7%) | 0.13 | 50 (34.5%) | 61 (16.4%) | **<0.001** |
| Fatigue/ malaise | 519 | 199 (38.3%) | 136 (51.9%) | 63 (24.5%) | **<0.001** | 88 (60.3%) | 111 (29.8%) | **<0.001** |
| Vomiting/ nausea | 519 | 41 (7.9%) | 31 (11.8%) | 10 (3.9%) | **<0.001** | 22 (15.1%) | 19 (5.1%) | **<0.001** |
| Abdominal pain | 519 | 60 (11.6%) | 35 (13.4%) | 25 (9.7%) | 0.20 | 24 (16.4%) | 36 (9.7%) | **0.03** |
| Chills | 519 | 61 (11.8%) | 42 (16.0%) | 19 (7.4%) | **0.002** | 24 (16.4%) | 37 (9.9%) | **0.04** |
| Loss of taste/ smell | 515 | 87 (16.9%) | 48 (18.6%) | 39 (15.2%) | 0.30 | 25 (17.2%) | 62 (16.8%) | 0.89 |
| Loss of appetite | 519 | 17 (3.3%) | 12 (4.6%) | 5 (1.9%) | 0.09 | 8 (5.5%) | 9 (2.4%) | 0.10 |
| **Clinical presentation** | | | | | | | | |
| Fever (>37.5C) | 518 | 68 (13.1%) | 45 (17.2%) | 23 (9.0%) | **0.006** | 20 (13.7%) | 48 (12.9%) | 0.81 |
| Hypothermia (≤35.0C) | 518 | 30 (5.8%) | 23 (8.8%) | 7 (2.7%) | 0.003 | 10 (6.8%) | 20 (5.4%) | 0.52 |
| Low oxygen level (<94%) | 481 | 91 (18.9%) | 55 (24.1%) | 36 (14.2%) | **0.006** | 64 (43.8%) | 27 (8.1%) | **<0.001** |
| **Appearance at enrollment** | 519 | | | | **<0.001** | | | **<0.001** |
| Acutely ill: non-ambulatory | | 79 (15.2%) | 49 (18.7%) | 30 (11.7%) | | 79 (54.1%) | 0 (0.0%) | |
| Acutely ill: ambulatory | | 145 (27.9%) | 133 (50.8%) | 12 (4.7%) | | 24 (16.4%) | 121 (32.4%) | |
| Healthy looking | | 295 (56.8%) | 80 (30.5%) | 215 (83.7%) | | 43 (29.5%) | 252 (67.6%) | |
| **Infectious co-morbidities** | | | | | | | | |
| Malaria[1]   Confirmed | | 7 (7.8%) | 6 (8.8%) | 1 (4.5%) | | 7 (11.5%) | 0 (0.0%) | |
| Suspected | 90 | 44 (48.9%) | 28 (41.2%) | 16 (72.7%) | **0.003** | 15 (24.6%) | 29 (100.0%) | **<0.001** |
| Negative | | 39 (43.3%) | 34 (50.0%) | 5 (22.7%) | | 39 (63.9%) | 0 (0.0%) | |
| Tuberculosis[3] | 518 | 4 (0.8%) | 1 (0.4%) | 3 (1.2%) | 0.37 | 2 (1.4%) | 2 (0.5%) | 0.32 |
| HIV[3] | 291 | 5 (1.7%) | 4 (4.0%) | 1 (0.5%) | 0.05 | 2 (2.9%) | 3 (1.3%) | 0.33 |
| Any infectious co-morbidity | 296 | 16 (5.4%) | 11 (10.5%) | 5 (2.6%) | **0.004** | 11 (15.1%) | 5 (2.2%) | **<0.001** |
| **Chronic co-morbidities** | | | | | | | | |
| Diabetes[2] | 519 | 40 (7.7%) | 20 (7.6%) | 20 (7.8%) | 0.95 | 28 (19.2%) | 12 (3.2%) | **<0.001** |
| High blood pressure (>130/80) | 508 | 163 (32.1%) | 56 (22.0%) | 107 (42.1%) | **<0.001** | 48 (33.6%) | 115 (31.5%) | 0.65 |
| Chronic cardiac disease history[2] | 514 | 18 (3.5%) | 13 (5.0%) | 5 (2.0%) | 0.06 | 12 (8.5%) | 6 (1.6%) | **<0.001** |
| Chronic pulmonary disease[2] | 518 | 9 (1.7%) | 2 (0.8%) | 7 (2.7%) | 0.10 | 2 (1.4%) | 7 (1.9%) | >0.99 |
| Current smoker[2] | 515 | 21 (4.1%) | 4 (1.5%) | 17 (6.7%) | **0.003** | 3 (2.1%) | 18 (4.8%) | 0.16 |
| Hypertension[2] | 518 | 77 (14.9%) | 39 (14.9%) | 38 (14.8%) | 0.99 | 42 (29.0%) | 35 (9.4%) | **<0.001** |
| Any chronic co-morbidity | 519 | 229 (44.1%) | 84 (32.1%) | 145 (56.4%) | **<0.001** | 78 (53.4%) | 151 (40.5%) | **0.008** |
| ≥2 chronic co-morbidities | 519 | 80 (15.4%) | 37 (14.1%) | 43 (16.7%) | 0.41 | 43 (29.5%) | 37 (9.9%) | **<0.001** |
| **Nutritional status[3]** | 470 | | | | 0.79 | | | 0.02 |
| Obese | | 84 (17.9%) | 48 (19.4%) | 36 (16.1%) | | 23 (21.5%) | 61 (16.8%) | |
| Overweight | | 166 (35.3%) | 85 (34.4%) | 81 (36.3%) | | 32 (29.9%) | 134 (36.9%) | |
| Normal weight | | 203 (43.2%) | 106 (42.9%) | 97 (43.5%) | | 43 (40.2%) | 160 (44.1%) | |
| Underweight | | 17 (3.6%) | 8 (3.2%) | 9 (4.0%) | | 9 (8.4%) | 8 (2.2%) | |
| **Anemia Status[4]** | | | | | | | | |
| Anemic | 213 | 26 (12.2%) | 19 (9.6%) | 7 (46.7%) | **<0.001** | 15 (25.0%) | 11 (7.2%) | **<0.001** |

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[1] RDTs were performed for inpatients suspected of having malaria by clinical staff; routine testing was not available. Suspected malaria refers to cases for whom no RDT was performed, who received anti-malarial medications taken prior to enrollment, and who reported chills and/or fever (measured or reported).

[2] Condition was self-reported by patient at enrollment.

[3] Obesity: in adults BMI >=30, in children up to 19 years old: BMI-for-age-z-score >3 SD.  Overweight: in adults BMI <30 and >=25, in children: BMI-for-age-z-score 2-2.99 SD. Underweight: in adults: BMI <18.5, in children <-2 SD. Children <5 (n=8) were excluded from this analysis, of them 0/7 with valid anthropometric measurements were malnourished by WHZ, and 2/7 were MAM by MUAC (>=11.5 cm & <12.5 cm).

[4] Children <12 years old: Hemoglobin < 11 g/dL, Children 12-15 years old: Hemoglobin < 12 g/dL, Non-pregnant women >=15 years old: Hemoglobin < 12 g/ dL, Pregnant women >=15 years old: Hemoglobin < 11 g/dL, Males >=15 years old: Hemoglobin <13 g/dL

14

**Table 3: Unadjusted and Adjusted Odds of Hospitalization by Select Patient Characteristics**

| | Unadjusted Odds | | | Adjusted Odds[1] | | |
|---|---|---|---|---|---|---|
| | Point Estimate | 95% CI | p-value | Point Estimate | 95% CI | p-value |
| **Demographic Characteristics** | | | | | | |
| Age (ref: age<45 years) | | | | | | |
|   Age 45-64 years | 2.24 | (1.45-3.47) | **<0.001** | 2.42 | (1.53-3.83) | **<0.001** |
|   Age 65+ years | 12.28 | (6.04-26.76) | | 12.16 | (5.67-26.09) | |
| Male sex (ref: female) | 0.80 | (0.53-1.19) | 0.27 | 0.93 | (0.59-1.46) | 0.76 |
| South Sudan (ref: DRC) | 0.55 | (0.38-0.82) | **0.003** | 0.77 | (0.45-1.33) | 0.35 |
| National (ref: non-nationals) | 2.90 | (1.67-5.05) | **<0.001** | 2.48 | (1.31-4.69) | **0.005** |
| **Primary Reason for Testing** | | | | | | |
| COVID-19 like symptoms (ref: other)[2] | 3.35 | (2.22-5.04) | **<0.001** | 2.59 | (1.62-4.16) | <0.001 |
| **Clinical Presentation at Enrollment** | | | | | | |
| Low oxygen level (<94%) | 8.90 | (5.34-14.85) | **<0.001** | 7.77 | (4.22-14.29) | **<0.001** |
| **Symptoms at Enrollment (self-reported)** | | | | | | |
| Symptomatic (ref: asymptomatic) | 4.19 | (2.36-7.46) | **<0.001** | 2.78 | (1.47-5.27) | **0.002** |
| Cough | 3.02 | (2.00-4.56) | **<0.001** | 2.27 | (1.43-3.62) | **<0.001** |
| Fatigue/malaise | 3.58 | (2.40-5.34) | **<0.001** | 2.80 | (1.77-4.41) | **<0.001** |
| Shortness of breath | 19.16 | (11-33.39) | **<0.001** | 21.37 | (10.91-41.87) | **<0.001** |
| Chest pain | 5.33 | (3.4-8.35) | **<0.001** | 4.48 | (2.71-7.43) | **<0.001** |
| Wheezing | 9.78 | (3.16-30.25) | **<0.001** | 8.34 | (2.42-28.67) | **<0.001** |
| Joint pain | 2.69 | (1.74-4.17) | **<0.001** | 2.08 | (1.25-3.46) | **0.005** |
| Loss of appetite | 2.34 | (0.89-6.2) | 0.07 | 1.52 | (0.52-4.42) | 0.44 |
| Runny Nose | 1.49 | (1.00-2.24) | 0.05 | 1.43 | (0.91-2.25) | 0.12 |
| Sore Throat | 2.22 | (1.45-3.39) | **<0.001** | 2.29 | (1.43-3.68) | **<0.001** |
| Headache | 1.72 | (1.17-2.53) | **0.006** | 1.36 | (0.88-2.12) | 0.17 |
| Nausea | 3.31 | (1.73-6.31) | **<0.001** | 2.88 | (1.42-5.85) | **0.003** |
| Abdominal pain | 1.84 | (1.06-3.21) | **0.032** | 1.73 | (0.95-3.17) | 0.07 |
| Diarrhea | 2.21 | (0.93-5.24) | 0.07 | 2.44 | (0.94-6.29) | 0.07 |
| Chills | 1.79 | (1.03-3.11) | **0.04** | 1.83 | (0.91-3.70) | 0.09 |
| **Exposure** | | | | | | |
| Visit to health care facility | 1.55 | (1.05-2.3) | **0.03** | 1.41 | (0.91-2.18) | 0.12 |
| Worked outside the home | 1.66 | (1.11-2.48) | **0.01** | 2.56 | (1.61-4.06) | **<0.001** |
| Health care worker | 0.49 | (0.22-1.07) | 0.07 | 0.46 | (0.20-1.06) | 0.07 |
| **Comorbidities** | | | | | | |
| Any infectious comorbidity | 7.74 | (2.59-23.1) | **<0.001** | 4.92 | (1.46-16.62) | **0.01** |
| Diabetes | 7.14 | (3.52-14.48) | **<0.001** | 5.08 | (2.28-11.32) | **<0.001** |
| Chronic cardiac disease | 5.63 | (2.07-15.31) | **<0.001** | 3.65 | (1.21-11.04) | **0.02** |
| Hypertension | 3.94 | (2.39-6.49) | **<0.001** | 2.65 | (1.45-4.85) | **0.002** |
| Chronic comorbidities (ref: none) [3] | | | | | | |
|   One chronic comorbidity | 1.00 | (0.63-1.6) | **<0.001** | 1.19 | (0.70-2.05) | **0.002** |
|   Two or more chronic comorbidities | 3.79 | (2.27-6.39) | | 3.11 | (1.62-5.96) | |
| **Nutrition** | | | | | | |
| Body mass index[4] | | | | | | |
|   Obesity (ref: normal weight) | 1.40 | (0.78-2.52) | **0.02** | 1.00 | (0.52-1.95) | **0.01** |
|   Overweight (ref: normal weight) | 0.89 | (0.53-1.48) | | 0.70 | (0.39-1.25) | |
|   Underweight (ref: normal weight) | 4.19 | (1.52-11.78) | | 5.04 | (1.63-15.57) | |
| Anemic[5] | 4.30 | (1.84-10.04) | **<0.001** | 10.69 | (3.32-34.41) | **<0.001** |

[1] Individual risk factor models adjusted for age, sex, country of enrollment and (non)national status (fixed effects) and facility (random effect)

[2] Included travel, close contact with a confirmed case, or other reason

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3    [3] Self-reported history of diabetes, chronic cardiac disease, chronic pulmonary disease, hypertension, asthma, current smoking,
4    or a blood pressure at enrollment of >130/80.
5    [4] Obesity: in adults BMI >=30, in children up to 19 years old: BMI-for-age-z-score >3 SD.  Overweight: in adults BMI <30 and >=25, in children: BMI-
6    for-age-z-score 2-2.99 SD. Underweight: in adults: BMI <18.5, in children <-2 SD. Children <5 (n=8) were excluded from this analysis, of them 0/7
7    with valid anthropometric measurements were malnourished by WHZ, and 2/7 were MAM by MUAC (>=11.5 cm & <12.5 cm).
8    5 Children <12 years old: Hemoglobin < 11 g/dL, Children 12-15 years old: Hemoglobin < 12 g/dL, Non-pregnant women >=15 years old:
9    Hemoglobin < 12 g/ dL, Pregnant women >=15 years old: Hemoglobin < 11 g/dL, Males >=15 years old: Hemoglobin <13 g/dL
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**Table 4: Unadjusted and Adjusted Odds of Mortality by Select Patient Characteristics**

| | Unadjusted Odds | | | Adjusted Odds[1] | | |
|---|---|---|---|---|---|---|
| | Point Estimate | 95% CI | p-value | Point Estimate | 95% CI | p-value |
| **Demographic Characteristics** | | | | | | |
| Age (ref: age<45 years) | | | | | | |
|   Age 45-64 years | 8.79 | (2.41-32.0) | **<0.001** | 11.42 | (3.06-3.06) | **<0.001** |
|   Age 65+ years | 37.35 | (11.02-171.55) | | 49.75 | (12.23-202.33) | |
| Male sex (ref: female) | 1.62 | (0.63-4.13) | 0.31 | 2.11 | (0.73-6.15) | 0.17 |
| South Sudan (ref: DRC) | 2.25 | (0.95-5.31) | **0.06** | 5.79 | (0.89-37.83) | 0.07 |
| National (ref: non-nationals) | 3.68 | (0.85-15.83) | **0.08** | 8.9 | (1.87-42.39) | **0.006** |
| **COVID-19 Testing** | | | | | | |
| COVID-19 symptoms (ref: other reason)[2] | 17.58 | (4.07-75.87) | **<0.001** | 13.44 | (2.83-63.76) | **0.001** |
| **Clinical Presentation at Enrollment** | | | | | | |
| Acutely ill: non-ambulatory[3] | 191.56 | (25.43-1443.3) | **<0.001** | 164.67 | (18.87-1437.13) | **<0.001** |
| Low oxygen level (<94%) | 41.13 | (11.98-141.16) | **<0.001** | 25.29 | (6.42-99.54) | **<0.001** |
| **Symptoms at Enrollment (self-reported)** | | | | | | |
| Symptomatic (ref: asymptomatic) | | | | | | |
| Cough | 5.08 | (1.72-15.02) | **0.003** | 3.33 | (1.03-10.79) | **0.05** |
| Fatigue/malaise | 7.04 | (2.6-19.08) | **<0.001** | 7.09 | (2.26-22.25) | **<0.001** |
| Shortness of breath | 66.32 | (15.31-287.34) | **<0.001** | 36.45 | (7.69-172.87) | **<0.001** |
| Chest pain | 11.21 | (4.55-27.62) | **<0.001** | 6.37 | (2.32-17.51) | **<0.001** |
| Loss of taste/smell | 2.45 | (1.02-5.87) | **0.05** | 1.59 | (0.56-4.54) | 0.39 |
| Wheezing | 12.68 | (4.3-37.42) | **<0.001** | 11.54 | (3.04-43.83) | **<0.001** |
| Joint pain | 2.16 | (0.93-5.02) | 0.08 | 1.10 | (0.42-2.90) | 0.84 |
| Loss of appetite | 7.05 | (2.12-23.47) | **0.001** | 5.17 | (1.13-23.69) | **0.04** |
| **Exposure** | | | | | | |
| Visit to health care facility | 2.77 | (1.22-6.29) | 0.02 | 2.08 | (0.78-5.55) | 0.14 |
| **Comorbidities** | | | | | | |
| Confirmed/suspect malaria (ref: negative) | 0.33 | (0.09-1.19) | 0.09 | 0.14 | (0.02-0.91) | **0.04** |
| History of diabetes | 12.60 | (5.26-30.2) | <0.001 | 4.49 | (1.59-12.63) | **0.004** |
| History of hypertension | 7.26 | (3.17-16.61) | <0.001 | 2.82 | (1.06-7.49) | **0.04** |
| High blood pressure (>130/80) | 2.85 | (1.27-6.43) | 0.01 | 1.66 | (0.64-4.32) | 0.30 |
| Num. of chronic comorbidities (ref: none)[4] | | | | | | |
|   One chronic comorbidity | 1.57 | (0.42-5.94) | <0.001 | 0.80 | (0.19-3.32) | **0.005** |
|   Two or more chronic comorbidities | 14.25 | (5.36-44.87) | | 4.96 | (1.51-16.31) | |

[1] Individual risk factor models adjusted for age, sex, country of enrollment and (non)national status (fixed effects) and facility (random effect)

[2] Included travel, close contact with a confirmed case, or other reason

[3] General appearance at enrollment classified by clinical staff at enrollment

[4] Self-reported history of diabetes, chronic cardiac disease, chronic pulmonary disease, hypertension, asthma, current smoking, or a blood pressure at enrollment of >130/80.

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│ 751 eligible per study protocol │
│    (357 – DRC, 394 – SSD)       │
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                                      ┌──────────────────────────┐
                                      │ 195 refusals             │
                                      │ (32 – DRC, 127 – SSD)    │
                                      └──────────────────────────┘
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│ 592 eligible per study protocol │
│    (325 – DRC, 267 – SSD)       │
└─────────────────────────────────┘
                                      ┌──────────────────────────────────┐
                                      │ 62 tested negative (57 – DRC, 5 – SSD) │
                                      │ 6 lost to follow-up (3 – DRC, 3 – SSD) │
                                      │ 5 transferred (3 – DRC, 2 – SSD)  │
                                      └──────────────────────────────────┘
┌─────────────────────────────────┐
│ 519 cases followed to discharge │
│    (262 – DRC, 257 – SSD)       │
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┌──────────────────────────┐      ┌──────────────────────────────┐
│ 144 enrolled in-patient  │      │ 375 enrolled out-patient[1]  │
│  (89 – DRC, 55 – SSD)    │      │  (173 – DRC, 202 – SSD)      │
└──────────────────────────┘      └──────────────────────────────┘
┌──────────────────────────────────────┐  ┌──────────────────────────────────────┐
│ 137 confirmed cases[2] (82 – DRC, 55 – SSD) │ │ 375 confirmed cases[2] (173 – DRC, 202 – SSD) │
│ 7 suspect cases[3] (7 – DRC, 0 – SSD) │  └──────────────────────────────────────┘
└──────────────────────────────────────┘
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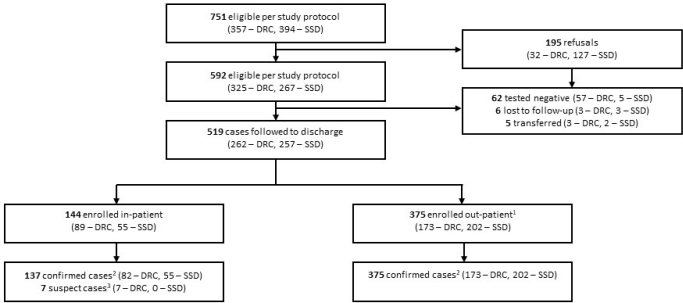
Figure 1. Study inclusion criteria flow chart
1 Of the 375 individuals enrolled outpatient, 2 individuals in South Sudan were subsequently admitted for in-patient care.
2 Cases were confirmed by real-time reverse transcription polymerase chain reaction (RT-PCR) (90% of confirmed cases) or antigen tests (10% of confirmed cases)
3 National case definitions were used to classify individuals as suspect cases. Of the suspect cases followed to discharge (n=7), 2 were never tested, 3 did not receive their test results, and 2 had specimens collected >3 days after enrollment.

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**Supplemental Table.** Characteristics of Health Facilities Enrolling Cases in this Study

| | Democratic Republic of the Congo | | | | South Sudan |
|---|---|---|---|---|---|
| **Hospital Location, Type and Study Enrollments** | | | | | |
| Location | Bukavu, South Kivu | Goma, North Kivu | Goma, North Kivu | Goma, North Kivu | Juba, Central Equatoria |
| Sector | Public | Public | Public | NGO operated | NGO operated |
| Study participants enrolled as inpatients | 25 | 0 | 42 | 22 | 55 |
| Study participants referred for home based care from facility catchment area | 64 | | 109[1] | | 202 |
| **Hospital Capacity** | | | | | |
| Doctors | 86 | 0 | 36 | 42 | 9 |
| Nurses | 168 | 7 | 92 | 86 | 33 |
| COVID care beds / Total beds[2] | 22/380 | NA | 20 / 220 | 28/220 | 82/82 |
| Clinical staff trained[3] | No | No | Yes | Yes | Yes |

[1] Study participants referred for home based care from throughout Goma, North Kivu. [2]The SSD facility was a COVID-19 only referral hospital and one of the Goma DRC facilities was an outpatient only facility; [3] Staff considered trained if they received information on COVID-19 case management and infection prevention and control (IPC) for COVID-19 prior to study initiation

# BMJ Open

## Risk Factors for Hospitalization and Death from COVID-19: A Prospective Cohort Study in South Sudan and Eastern Democratic Republic of the Congo

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# Risk Factors for Hospitalization and Death from COVID-19: A Prospective Cohort Study in South Sudan and Eastern Democratic Republic of the Congo

By

Eva Leidman[1,3]*, Shannon Doocy[3]*, Grace Heymsfield[1], Abdou Sebushishe[2], Eta Ngole Mbong [2], Jennifer Majer[2], the IMC-CDC COVID-19 Research Team[4] and Iris Bollemeijer[2]

[1] US Centers for Disease Control and Prevention, Atlanta, GA

[2] International Medical Corps – US, South Sudan, DR Congo Offices

[3] Johns Hopkins Bloomberg School of Public Health, Baltimore MD, USA

[4] The study team included Deepak Kumar, Kelechi Udoh from IMC S South Sudan, Dugsiye Ahmed, Arsene Baleke, from IMC DR Congo, Jennifer Majer from IMC US, and Aimee Summers from the US CDC

*Corresponding authors

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**\*Correspondence:**

Eva Leidman, Epidemiologist, Centers for Disease Control and Prevention, 1600 Clifton Rd Atlanta, GA 30329. Email: eleidman@cdc.gov.

Shannon Doocy, Associate Professor, Dept. of International Health, Johns Hopkins Bloomberg School of Public Health, 615 N Wolfe St, Suite E8132, Baltimore, MD, USA. Email: doocy1@jhu.edu.

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# Abstract

**Objectives**: Our study described demographic characteristics, exposures, and symptoms, and comorbidities to evaluate risk factors of hospitalization and mortality among cases in Juba, South Sudan (SSD) and North and South Kivu in eastern Democratic Republic of the Congo (DRC).

**Design** Prospective observational cohort of COVID-19 cases

**Methods** Individuals presenting for care at one of five study facilities in SSD (n=1) or DRC (n=4) or referred from home-based care by mobile medical teams between December 2020– June 2021 were eligible for enrollment. Demographic characteristics, COVID-19 exposures, symptoms at presentation, as well as acute and chronic comorbidities were evaluated using a standard questionnaire at enrollment. Disease progression was characterized by location of care using mixed-effects regression models.

**Results** 751 individuals were eligible for enrollment. Among cases followed to discharge or death (n=519), 375 were enrolled outpatients (75.7%). A similar number of cases were enrolled in DRC (n=262) and South Sudan (n=257). Overall mortality was 4.8% (95% CI: 3.2-6.9%); there were no outpatient deaths. Patients presenting with any symptoms had higher odds of hospitalization [adjusted odds ratio (AOR) 2.78, 95% CI 1.47 −5.27] and all deaths occurred among symptomatic individuals. Odds of both hospitalization and mortality were greatest among cases with respiratory symptoms; presence of low oxygen levels on enrollment was strongly associated with both hospitalization (AOR 7.77, 95% CI: 4.22− 14.29) and mortality (AOR 25.29, 95% CI 6.42− 99.54). Presence of more than one chronic comorbidity was associated with 4.96 (95% CI 1.51− 16.31) times greater odds of death; neither infectious comorbidities evaluated, nor malnutrition, were significantly associated with increased mortality.

**Conclusions** Consistent with prior literature, older age, low oxygen level, other respiratory symptoms, and chronic comorbidities were all risk factors for mortality. Patients presenting with these characteristics were more likely to be hospitalized, providing evidence of effective triage and referral.

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## Strengths and limitations of this study

- A prospective observational cohort study enrolled COVID-19 cases in South Sudan and the Democratic Republic of Congo to better characterize risk factors of hospitalization and death.
- Cases admitted for care at inpatient health facilities as well as cases managed by home-based care teams were enrolled in the study, such that the study population represent the spectrum of severity of COVID-19 cases.
- Given barriers to case identification in both countries, particularly limited testing capacity, the study population represents only cases who interacted with the health system, the principal limitation of this study.

4

# Introduction

Characterizing risk factors for severe Coronavirus disease (COVID-19) is critical for identifying individuals who may benefit from increased monitoring, hospitalization, or ventilator support, as well as those at increased risk of death.[1,2,3] Early identification and referral is particularly important in resource scarce contexts where access to inpatient care is limited. Risk factors for severe illness from COVID-19 with strong evidence supported by systematic reviews and meta-analyses include cancer, cerebrovascular disease, chronic kidney disease, chronic obstructive pulmonary disease, diabetes mellitus, cardiovascular disease, obesity, pregnancy, and smoking.[4,5,6,7] Demographic risk factors, including older age and male sex, have also been associated with poor prognosis.[1,2]

The evidence on risk factors for severe COVID-19 primarily includes case surveillance and studies conducted in higher income settings.[8] Consequently, less is known regarding how these risk factors, as well as undernutrition and exposure to infectious conditions more prevalent in lower resource settings, impact the severity of COVID-19. This evidence gap is particularly relevant given differences in the epidemiology of COVID-19 in Africa, where officially reported numbers of cases and deaths are lower than the Americas, Europe, and Asia[9] , while case fatality rates are estimated to be higher. Modeled estimates of excess mortality for patients admitted for critical care in Africa are between 11 and 23 excess deaths per 100 admissions compared with the global average mortality from COVID-19.[10] This research aimed to characterize early symptoms, exposures, comorbidities, and other risk factors associated with hospitalization and death from COVID-19 in Juba, South Sudan (SSD) and North and South Kivu, Eastern Democratic Republic of Congo (DRC) to inform identification and triage of COVID-19 cases at higher risk of mortality in resource-poor and humanitarian settings in Africa.

# Methods

An observational cohort study of COVID-19 cases enrolled between December 2020–June 2021; the last cases were discharged in July 2021 in both countries. Five study facilities operated or supported by International Medical Corps (IMC) recruited patients, including a COVID-19 treatment center in Juba, SSD and four health facilities in Eastern DRC. Study facilities in DRC included general public hospitals in Bukavu and Goma, as well as a public outpatient clinic and an NGO operated health center in Goma. Characteristics of the study facilities and care offered are described in the **Supplemental Table**. Availability of therapies for inpatients are presented by facility in a companion manuscript from this study focused on inpatient management.[11] Available therapies for outpatients were limited. Individuals presenting for care at a study facility or referred from home-based care by mobile medical teams in the facility catchment area were eligible. Cases with a positive real-time reverse transcription polymerase chain reaction (RT-PCR) or antigen test and inpatients not tested meeting the national suspect case definitions[*] were eligible for enrollment. Cases were excluded from analysis if they tested negative following enrollment, were lost to follow-up (before recovery or death), or were transferred to another facility for care.

Oral consent was obtained for eligible adults and parental consent for children <18 years. Additionally, assent was obtained for children 12–17 years. Participants receiving inpatient care were followed up daily, whereas outpatients were followed up weekly through home visits and/or phone interviews. All participants were followed until COVID-19 recovery, death, or loss to follow-up. Inpatients were follow-up daily whereas outpatient cases were followed weekly. Cases treated as inpatient were considered

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[*] In DRC, a case met the syndromic case definition if they had one or more of the following sign(s) or symptom(s): fever, dry cough, headache, severe fatigue, sore throat, shortness of breath, dyspnea (difficulty breathing), muscle or joint pain, or coryza (common cold). In South Sudan, suspect cases presented with acute onset of fever ≥38°C and cough, or an acute onset of any three or more signs or symptoms, including those in the DRC case definition as well as anorexia, nausea, vomiting, diarrhea, and altered mental status.

5

recovered if they were discharged alive from inpatient care. Patients treated at home were considered recovered if they met one of the following conditions: resolution of fever for at least 48 hours without the use of fever-reducing medications and with improvement of other symptoms; or asymptomatic at two sequential follow-up visits. For outpatients, three attempts to contact were made before an individual was considered lost to follow-up.

Data on sociodemographic characteristics, COVID-19 exposures and symptoms, self-reported health history, anthropometric measurements, and SARS-COV-2 tests (RT-PCR and/or antigen) were collected at enrollment by research nurses using a standard data collection instrument. Anthropometric measures of mid-upper arm circumference (MUAC), weight, height, and edema were assessed using standard procedures.[12] Malaria was evaluated using a rapid diagnostic test if ordered per the facility's standard operating procedures. Other infectious diseases – human immunodeficiency virus (HIV) and Tuberculosis (TB) – were self-reported. Hemoglobin A1c (HbA1c) was measured using an at home test kit for individuals who reported history of diabetes. Oxygen saturation, pulse rate, and perfusion index were evaluated using the Masimo Rad 57 or Multi-parameter Patient Monitor[†][13,14] Hemoglobin concentration was evaluated using either a HemoCue 301 or Masimo Rad 57 device.[‡] Anemia and nutritional status were classified based on World Health Organization (WHO) cutoffs.[15,16,17,18] Cutoffs for other clinical conditions, including poorly controlled diabetes (HbA1c>8.0%) and low oxygen levels (<94%) were defined to align with national treatment guidelines and case definitions.

In DRC, data was recorded on paper and subsequently uploaded to CommCare, a secure online data collection platform for collecting longitudinal patient data, and in SSD, data were directly entered. Analyses were conducted using R (version 4.0.4). Distributions of continuous variables were compared by country of enrollment and hospitalization status using Kruskal-Wallis test, Fisher's exact test was used for categorical parameters. All demographic characteristics, COVID-19 exposures, symptoms, vital signs, and comorbidities evaluated as risk factors for hospitalization and mortality are presented in Table 1 and 2; parameters are presented as they were parameterized in models. Parameters were significant at p<0.1 in unadjusted models were evaluated in generalized linear mixed models (GLMM) for mortality and hospitalization; patients were considered hospitalized if ever admitted into inpatient care while enrolled in the study. Two-level GLMMs were fitted using a logit link to account for the expected correlation in outcomes within health facilities which may be observed given differences in access to medication, staffing, or quality of care available at each facility. Given the large number of risk factors of interest, separate models were built for each risk factor additionally adjusted for patient age, sex, country of enrollment, and nationality as fixed effects; results are reported as adjusted odds ratios (AOR) with 95% CIs with a p-value of <0.05 considered significant.

This study was reviewed and approved by the Johns Hopkins University Institutional Review Board, the South Sudan Ministry of Health Ethics Committee, the University of Kinshasa School of Public Health , and the US CDC. The study is registered with ClinicalTrials.gov (NCT04568499). The final datasets are archived on Humanitarian Data Exchange.[19] The study was funded by USAID (award 72OFDA20GR0221). USAID had no role in the conceptualization, design, data collection, analysis, interpretation, and drafting of study findings.

## Patient and Public Involvement

Patients with COVID-19 and their families were not involved in setting the research question, outcome measures, design and implementation of the study given the emergency nature of the study. However,

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[†] Both devices were used in DRC. The Multi-parameter Patient Monitor -YK8000K was used in South Sudan throughout the study.

[‡] Masimo devices were used at facilities in DRC between April and June 2021. The HemoCue was used between December 2020 and April 2021 in DRC and throughout the study in South Sudan.

6

patients and their families were involved in dissemination of the findings at interim points throughout the study which helped to inform triage, referral, and care in the enrolling countries.

## Results

During the study period, 751 individuals were eligible per the study protocol of which 592 (78.8%) consented to participate **(Figure 1)**. Among cases followed to discharge (n=519), 375 were enrolled as outpatients (75.7%) of which all were confirmed cases and 144 were enrolled inpatient (24.3%) of which 137 were confirmed and 7 were suspect cases. Similar numbers of cases were followed to discharge (recovery or death) in SSD (n=257) and DRC (n=262). Patients were followed up for an average of 8.9 days for a total of 4,630 days of follow-up time.

Patient demographics, exposure history, symptoms at enrollment, and clinical history differed by country **(Table 1)**. SSD had significantly fewer nationals (58.3% vs 94.3%, p<0.001) and female cases (24.9% vs. 41.6%, p<0.001). There was no significant difference in mean age by country, however, the proportion of individuals >65 years was slightly higher in DRC (9.9% vs 6.6%). Cases in SSD were more likely to work outside the home (35.8% vs 26.3%, p=0.020); otherwise, risk factors for exposure were similar. Cases in DRC were more likely to present with symptoms (92.7% vs 54.5%, p<0.001), likely a function of testing protocols. The majority of cases in SSD were identified by travel screening (53.4%), whereas in DRC most participants sought testing after experiencing COVID-19 like symptoms (53.4%). Overall, the most common symptoms were cough (52.4%), headache (43.4%), fatigue/malaise (38.3%), and runny nose (30.9%) **(Table 2)**.

Evaluating differences in characteristics of hospitalized patients was a primary aim given that a minority of cases (28.1%) ever received inpatient care. Participants in DRC were more likely to be hospitalized (34.0% vs 22.2%, p=0.003), likely due in part to differences in case identification by country. Hospitalized patients were older than outpatients (mean age 48.0 vs 37.7 years, p<0.001) and more likely to be a national of the country of enrollment (88.2% vs 72.0%, p<0.001). Hospitalized patients were also more likely than outpatients to have been tested due to COVID-19 like symptoms (60.9% vs 31.7%, p<0.001), and for almost all symptoms assessed, a significantly higher proportion of cases among inpatients self-reported experiencing the symptom than among outpatient (**Table 2**).

The prevalence of infectious comorbidities (i.e., malaria, tuberculosis, and/or HIV) overall was low (5.4%), however, hospitalized cases were more likely to present with one or more of the assessed infectious comorbidities (15.1% vs 2.2%, p<0.001); all confirmed malaria cases (n=7) were hospitalized. Chronic comorbidities were more prevalent, with 44.1% of persons presenting with at least one chronic comorbidity and 15.4% presenting with two or more chronic comorbidities. Chronic comorbidities were more common among hospitalized patients (53.4% vs 40.5%, p<0.008).High blood pressure was the most frequently reported chronic comorbidity, with similar prevalence between inpatients and outpatients (p=0.65). Obesity and self-reported history of hypertension, diabetes, and chronic cardiac disease all were significantly more prevalent among hospitalized cases (p<0.02 for all comparisons). Among individuals with diabetes history for whom HbA1c values were available (n=28), diabetes was poorly controlled (HbA1c>8.0%) for 32.1%; neither differences by country nor by hospitalization were significant. Anemia was also more common (25.0% vs 7.2%, p<0.001) among hospitalized cases.

Overall, the mortality proportion was 4.8% (CI: 3.2-6.9%). The mortality proportion was 17.1% (CI: 11.6-23.8%) among patients ever hospitalized; there were no outpatient deaths. All deceased individuals were symptomatic at enrollment and classified by clinical staff as acutely ill and non-ambulatory; as such, estimates are unadjusted for severity at enrollment. Mortality was higher in South Sudan (6.6%) than DRC (3.3%), and this difference was marginally significant (p=0.058). Regression models evaluated the adjusted

7

odds ratio of hospitalization (**Table 3**) and mortality (**Table 4**). Age and nationality were the only demographic characteristics significantly associated with hospitalization and mortality. Odds of hospitalization were 12.16 (CI: 5.67 −26.09) times greater among older individuals (≥65 years) compared with individuals <45 years of age; odds of mortality were 49.75 (CI 12.23 −202.33) times greater for older adults. Nationals had 2.48 (CI: 1.31 −4.69) times higher odds of hospitalization and 8.90 (95% CI: 1.87 − 42.39) times higher odds of mortality than patients that were not nationals of the country of enrollment.

Patients presenting with any symptoms had higher odds of hospitalization (AOR 2.78, CI 1.47 −5.27) and all deaths occurred among symptomatic individuals. Hospitalization and mortality AORs were significant for cough, fatigue, shortness of breath (SOB), chest pain, and wheezing. Joint pain, sore throat, and nausea were significantly associated with hospitalization but not mortality. Loss of appetite was significantly associated with mortality but not hospitalization. The magnitude of the effect was greatest for respiratory symptoms: SOB (hospitalization AOR 21.37, CI: 10.91− 41.87; mortality AOR 36.45, CI: 7.69 −172.87) and wheezing (hospitalization AOR 8.34, CI: 2.42− 28.67; mortality AOR 11.54, CI 3.04− 43.83). Consistently, presence of oxygen levels <94% at enrollment was strongly associated with both hospitalization and death (hospitalization AOR 7.77, CI: 4.22− 14.29; mortality AOR 25.29, 95% CI 6.42− 99.54). Among patients classified by research nurses as acutely ill and non-ambulatory on enrollment, all were hospitalized; this classification was the strongest risk factor for mortality (AOR 164.67, CI 18.87− 1437.13).

Infectious co-morbidities (malaria, TB, HIV) were only associated with increased hospitalization when analyzed as a single aggregated risk factor for presence of any assessed co-infectious disease. Presence of confirmed or suspected malaria was associated with a decreased odds of death (AOR 0.14, CI: 0.02− 0.91). History of diabetes and hypertension were both significantly associated with increased risk for hospitalization and death (p<0.005 for all comparisons). Presence of more than one chronic comorbidity was associated with 3.11 (CI 1.62− 5.96) times greater odds of hospitalization and 4.96 (CI 1.51− 16.31) odds of death. Underweight and anemia were significantly associated with hospitalization risk (underweight AOR 5.04, CI: 1.63-15.57; Anemia AOR 10.69, CI: 3.32-34.41) but not mortality.

## Discussion

Consistent with reports from other African settings,[20,21] among our sample of 519 COVID-19 patients in Eastern DRC and Juba, there were nearly three times as many patients enrolled as outpatients. Outpatients ultimately experienced no deaths during the study period. Case fatality reported in our observational cohort study (4.8%) was consequently closer to estimates from national case surveillance in DRC (1.9%), South Sudan (1.1%) and Africa overall (2.4%) as well as studies of outpatients from other settings (1.3%) than estimates among hospitalized cases; among patients admitted to intensive care units in Africa, case fatality has been estimated to approach 50%.[10,22]

Given both supply and demand barriers to facility-based treatment, WHO recommends that in cases where it is not possible to isolate all laboratory confirmed cases in a health care facility, groups with the highest risk of poor outcomes should be prioritized.[23] Our study provides information about the profile of patients receiving home-based care in resource poor African settings that can inform case management strategies.

Age and nationality of patients receiving home-based care differed significantly from those receiving inpatient care and both characteristics were significantly associated with odds of mortality, consistent with prior research; however, sex was not associated with either hospitalization or mortality. Older age has been well established as a strong predictor of severity and clinical outcomes from COVID-19[24], and as such, referral of older individuals for inpatient care is recommended in national protocols and global guidance. Differences in both hospitalization and survival by nationality, where SSD/DRC nationals faced

8

increased risk compared to non-nationals, likely reflect differences in case identification, care seeking, as well as sociodemographic characteristics of these populations, as explored in the qualitative research that complemented this study.[11] The finding of no sex differences is in contrast with prior meta-analysis that have found men at higher risk of severe disease; however, a 2021 study of inpatients in Africa similarly found no sex differences in mortality.[24,25,26] It is possible that greater differences in exposure and care seeking by gender in these settings confound the association between sex and severity.

In addition to age, current WHO guidance recommends that individuals who smoke, are obese, or have a history of cardiovascular disease, diabetes mellitus, chronic lung disease, are at greater risk for poor outcomes from COVID-19 and should be referred for inpatient care. [23] However, neither individuals who smoked, were obese, or had chronic lung disease in our study were significantly more likely to be treated inpatient, suggesting a potential opportunity to improve triage and referral. Interestingly, study subjects classified as being underweight and anemic were both more likely to be hospitalized but did not face increased risk of death. However, anthropometric measurements frequently could not be collected for patients who were non-ambulatory at admission; the association between availability of anthropometric measurements and clinical severity of COVID-19 at admission maybe confounding this effect. Evidence regarding anemia and poor COVID-19 outcomes from prior meta-analyses is mixed.[27,28] We did not observe the 'j-shape' relationship between body mass index (BMI) and mortality reported in prior meta-analysis.[29] Additionally, consistent with prior literature,[30] history of hypertension was strongly associated with increased risk of both hospitalization and mortality, suggesting the need to screen for hypertension at initial patient consultation.

Triage of patients at risk of severe outcomes remains predominantly based on history of chronic conditions given the preponderance of evidence related to these conditions. While several cohort studies and case series suggest that individuals with HIV are at increased risk of severe outcomes,[1] and that tuberculosis and malaria may confer an increased risk of COVID-19 co-infection,[31,32] evidence on infectious comorbidities is more limited than that for chronic comorbidities. Given higher prevalence of these conditions in our target populations in DRC (HIV=1.2%[33], TB=0.3%[34], malaria=32.6%[35]) and South Sudan (HIV=2.5%[36], TB=0.1%[37], malaria=27.2%[35]) than in high income countries, gathering evidence on these conditions was a core aim of this study. However, our final samples of individuals with HIV (n=5), TB (n=4) and suspected (n=44) or confirmed (n=7) malaria were all small. Given these small samples, presence of infectious comorbidities was only a significant predictor of hospitalization when pooled. Malaria was significantly negatively associated with mortality, however, findings should be interpreted with caution given potential biases in case identification given universal testing was not conducted as part of the study protocol.

Patients presenting with evidence of respiratory symptoms were at greatest risk of death. Individuals with low oxygen levels and clinical assessment of non-ambulatory (generally in respiratory distress) had 25- and 164-times greater odds of mortality, respectively. These data suggest these high-risk individuals were being successfully triaged for inpatient care, potentially due to ability to measure oxygen among outpatients using pulse oximeters made available by the study. In August 2020, WHO revised guidance on home-based management to recommend use of home pulse oximetry as a safe, non-invasive tool for early identification of low oxygen levels in patients with initially mild or moderate COVID-19.[23] This approach is not yet universal practice in many low-income settings including South Sudan and DRC and this research suggests a need to advocate for their adoption and scale-up in resource-poor settings. Self-reported respiratory symptoms at admission (shortness of breath, wheezing, and chest pain) were also associated with increased odds of mortality which is indicative of the need for a standardized approach to respiratory assessment in outpatient screening. The strength of the associations between respiratory symptoms and mortality may be informative to improve patient triaged in these settings.

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Our study is subject to five principal limitations. First, the study population reflects only patients with COVID-19 who interacted with the health system; given many barriers to case identification (including weak surveillance systems, limited COVID-19 testing capacity, and sub-optimal care seeking behaviors) the cases identified for recruitment are a subset of COVID-19 cases and may not be representative of all the caseload in the target population.[38] In particular, while both countries had similar national protocols for prioritization of specimens for testing, a much larger proportion of specimens tested in South Sudan were among travelers; the larger proportion of travelers, most of whom were asymptomatic or had only mild symptoms, in South Sudan than in DRC is reflected in our sample. Second, among eligible individuals, 76.7% in SSD and 15.6% in DRC could not be reached given invalid or missing phone numbers and addresses; identification and enrollment of outpatients was particularly challenging, and limitations likely resulted in further sampling bias. Thirdly, inability to rapidly scale study staff during the February/March 2021 surge and a health worker strike in SSD, and in DRC security issue, and the May 22, 2021 eruption of Mt. Nyiragongo in DRC contributed to a smaller sample than planned (n=1000), reducing power to identify other potentially significant risk factors. Fourth, infectious comorbidities were self-reported, potentially resulting in under-detection; these conditions were rarely observed in the final sample and the study lacked power to adequately assess their relationship with adverse COVID-19 outcomes. Finally, to ensure rigorous supervision the study sites were all operated or supported by IMC and may therefore be better resourced than other health facilities in the two countries.

## Conclusions

Risk factors for mortality observed in our study were generally consistent with those identified in the current WHO guidance on clinical evaluation of COVID-19 patients for risk factors of severe disease based on evidence from higher income settings.[23] Individuals who were older, presenting with low oxygen levels, or reporting a history of diabetes, chronic cardiac disease, and hypertension were more likely to be hospitalized suggesting successful triage and referral of patients at increased risk of death. Individuals with evidence of respiratory distress – as reported by the patient, evaluated by clinical staff, or presenting with low oxygen – were at greatest risk of mortality. Given small samples, evaluation of individual infectious comorbidities, anemia and wasting is limited; however, pooled data suggests increased risk of hospitalization but not mortality.

The evaluation of risk factors for severe COVID-19 presented in this study may be informative for developing locally adapted tools for improving patient triage and referral, to support efforts to reduce morbidity and mortality in these settings. Similar tools to support community case managers in identifying children at greatest need for clinical management have been effective for childhood illnesses.[39] Triage and referral efforts may be most impactful where mobile medical teams are provided equipment to evaluate oxygen levels and assess symptoms of respiratory distress.

10

**Disclaimer**: The findings and conclusions are those of the authors and do not necessarily represent the official position of their respective institutions.

**Contributorship**: EL, SD, AS, ENM, JM, and IB made substantial contributions to the conception or design of the work. ENM and JM contributed to acquisition, and EL, SD, GH, contributed to analysis and interpretation of data for the work. EL and SD drafting the manuscript; GH, AS, ENM, JM, and IB revising it critically for important intellectual content. All authors gave final approval of the version to be published and agree to be accountable for the accuracy or integrity of the work.

**Ethics approval:** This study was reviewed and approved by the Johns Hopkins University Institutional Review Board (IRB number: IRB00000758), the South Sudan Ministry of Health Ethics Committee, the University of Kinshasa School of Public Health, and the US CDC.

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**Figure 1. Study inclusion criteria flow chart**

*(Figure uploaded as a separate jpg file)*

[1] Of the 375 individuals enrolled outpatient, 2 individuals in South Sudan were subsequently admitted for in-patient care.
[2] Cases were confirmed by real-time reverse transcription polymerase chain reaction (RT-PCR) (90% of confirmed cases) or antigen tests (10% of confirmed cases)
[3] National case definitions were used to classify individuals as suspect cases. Of the suspect cases followed to discharge (n=7), 2 were never tested, 3 did not receive their test results, and 2 had specimens collected >3 days after enrollment.

12

**Table 1. Demographics characteristics and exposures of patients, by country and location of treatment**

| | | All participants | By Enrollment Country | | | By Location of Treatment | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | | | DR Congo, N=262 | S Sudan, N=257 | p-value | Ever Hospitalized, N=146 | Never Hospitalized, N=373 | p-value |
| | N | n (%) | n (%) | n (%) | | n (%) | n (%) | |
| **Age (years)** (Mean, SD) | 519 | 40.6 ±15.6 | 40.2 ± 17.8 | 41.1 ± 12.9 | 0.45 | 48.0 ±18.8 | 37.7 ± 13.0 | **<0.001** |
| **Age categories (years)** | 519 | | | | **<0.001** | | | **<0.001** |
| < 18 | | 21(4.0%) | 20(7.6%) | 1(0.4%) | | 5(3.4%) | 16(4.3%) | |
| 18-44 | | 308(59.3%) | 139(53.1%) | 169(65.8%) | | 58(39.7%) | 250(67.0%) | |
| 45-64 | | 147(28.3%) | 77(29.4%) | 70(27.2%) | | 51(34.9%) | 96(25.7%) | |
| 65+ | | 43(8.3%) | 26(9.9%) | 17(6.6%) | | 32(21.9%) | 11(2.9%) | |
| **Sex** | 519 | | | | **<0.001** | | | 0.27 |
| Male | | 346(66.7%) | 153(58.4%) | 193(75.1%) | | 92(63.0%) | 254(68.1%) | |
| Female | | 173(33.3%) | 109(41.6%) | 64(24.9%) | | 54(37.0%) | 119(31.9%) | |
| **Nationality** | 516 | | | | **<0.001** | | | **<0.001** |
| National (DRC/ SSD) | | 395(76.6%) | 247(94.3%) | 148(58.3%) | | 127(88.2%) | 268(72.0%) | |
| African country | | 68(13.2%) | 8(3.1%) | 60(23.6%) | | 7(4.9%) | 61(16.4%) | |
| Non-African country | | 53(10.3%) | 7(2.7%) | 46(18.1%) | | 10(6.9%) | 43(11.6%) | |
| **Study Site** | 519 | | | | | | | 0.004 |
| Juba | | 257(49.5%) | — | 257(100.0%) | | 57(39.0%) | 200(53.6%) | |
| North Kivu | | 173(33.3%) | 173(66.0%) | — | | 64(43.8%) | 109(29.2%) | |
| South Kivu | | 89(17.1%) | 89(34.0%) | — | | 25(17.1%) | 64(17.2%) | |
| **Reason for testing** | 491 | | | | **<0.001** | | | **<0.001** |
| COVID-19 symptoms | | 196(39.9%) | 127(53.4%) | 69(27.3%) | | 84(60.9%) | 112(31.7%) | |
| Known COVID exposure | | 71(14.5%) | 33(13.9%) | 38(15.0%) | | 12(8.7%) | 59(16.7%) | |
| Travel | | 211(43.0%) | 76(31.9%) | 135(53.4%) | | 40(29.0%) | 171(48.4%) | |
| Other | | 13(2.6%) | 2(0.8%) | 11(4.3%) | | 2(1.4%) | 11(3.1%) | |
| **Risk of Exposure** | | | | | | | | |
| Work outside the home | 519 | 161(31.0%) | 69(26.3%) | 92(35.8%) | **0.02** | 57(39.0%) | 104(27.9%) | **0.01** |
| Health care worker | 516 | 48(9.3%) | 29(11.1%) | 19(7.5%) | 0.15 | 8(5.6%) | 40(10.8%) | 0.07 |
| Visit to health care facility[1] | 517 | 188(36.4%) | 85(32.6%) | 103(40.2%) | 0.07 | 64(43.8%) | 124(33.4%) | **0.03** |
| Caring for COVID patient | 506 | 14(2.8%) | 6(2.4%) | 8(3.2%) | 0.58 | 3(2.1%) | 11(3.0%) | 0.77 |
| Contact with a COVID case | 262 | 80(30.5%) | 48(35.6%) | 32(25.2%) | 0.07 | 15(26.3%) | 65(31.7%) | 0.43 |

[1] As a health care worker and/or as a care provider to a family/ friend/ caregiver, within the past four weeks

**Table 2. Symptoms, comorbidities and risk factors reported at enrollment, by country and location of treatment**

| | | All patients | By Enrollment Country | | | By Location of Treatment | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | | | DR Congo, N=262 | S Sudan, N=257 | p-value | Ever Hospitalized N=146 | Never Hospitalized N=373 | p-value |
| | N | n (%) | n (%) | n (%) | | n (%) | n (%) | |
| **Primary Outcomes** | | | | | | | | |
| Ever hospitalized | 519 | 146 (28.1%) | 89 (34.0%) | 57 (22.2%) | **0.003** | -- | -- | -- |
| Died | 519 | 25 (4.8%) | 8 (3.1%) | 17 (6.6%) | 0.06 | 25 (17.1%) | 0 (0.0%) | **<0.001** |
| **Symptoms (self-reported)** | | | | | | | | |
| Symptomatic | 519 | 383(73.8%) | 243(92.7%) | 140(54.5%) | **<0.001** | 131(89.7%) | 252(67.6%) | **<0.001** |
| Cough | 519 | 272(52.4%) | 176(67.2%) | 96(37.4%) | **<0.001** | 104(71.2%) | 168(45.0%) | **<0.001** |
| Sore throat | 518 | 127(24.5%) | 54(20.7%) | 73(28.4%) | **0.04** | 52 (35.9%) | 75 (20.1%) | **<0.001** |
| Runny nose | 518 | 160 (30.9%) | 106 (40.6%) | 54 (21.0%) | **<0.001** | 54 (37.2%) | 106 (28.4%) | 0.05 |
| Shortness of breath | 519 | 96 (18.5%) | 51 (19.5%) | 45 (17.5%) | 0.57 | 76 (52.1%) | 20 (5.4%) | **<0.001** |
| Wheezing | 519 | 18 (3.5%) | 12 (4.6%) | 6 (2.3%) | 0.16 | 14 (9.6%) | 4 (1.1%) | **<0.001** |
| Chest pain | 518 | 110 (21.2%) | 63 (24.1%) | 47 (18.3%) | 0.10 | 63 (43.4%) | 47 (12.6%) | **<0.001** |
| Headache | 518 | 225 (43.4%) | 154 (59.0%) | 71 (27.6%) | **<0.001** | 77 (53.1%) | 148 (39.7%) | **0.006** |
| Muscle/ joint pain | 518 | 111 (21.4%) | 63 (24.1%) | 48 (18.7%) | 0.13 | 50 (34.5%) | 61 (16.4%) | **<0.001** |
| Fatigue/ malaise | 519 | 199 (38.3%) | 136 (51.9%) | 63 (24.5%) | **<0.001** | 88 (60.3%) | 111 (29.8%) | **<0.001** |
| Vomiting/ nausea | 519 | 41 (7.9%) | 31 (11.8%) | 10 (3.9%) | **<0.001** | 22 (15.1%) | 19 (5.1%) | **<0.001** |
| Abdominal pain | 519 | 60 (11.6%) | 35 (13.4%) | 25 (9.7%) | 0.20 | 24 (16.4%) | 36 (9.7%) | **0.03** |
| Chills | 519 | 61 (11.8%) | 42 (16.0%) | 19 (7.4%) | **0.002** | 24 (16.4%) | 37 (9.9%) | **0.04** |
| Loss of taste/ smell | 515 | 87 (16.9%) | 48 (18.6%) | 39 (15.2%) | 0.30 | 25 (17.2%) | 62 (16.8%) | 0.89 |
| Loss of appetite | 519 | 17 (3.3%) | 12 (4.6%) | 5 (1.9%) | 0.09 | 8 (5.5%) | 9 (2.4%) | 0.10 |
| **Clinical presentation** | | | | | | | | |
| Fever (>37.5C) | 518 | 68 (13.1%) | 45 (17.2%) | 23 (9.0%) | **0.006** | 20 (13.7%) | 48 (12.9%) | 0.81 |
| Hypothermia (≤35.0C) | 518 | 30 (5.8%) | 23 (8.8%) | 7 (2.7%) | 0.003 | 10 (6.8%) | 20 (5.4%) | 0.52 |
| Low oxygen level (<94%) | 481 | 91 (18.9%) | 55 (24.1%) | 36 (14.2%) | **0.006** | 64 (43.8%) | 27 (8.1%) | **<0.001** |
| **Appearance at enrollment** | 519 | | | | **<0.001** | | | **<0.001** |
| Acutely ill: non-ambulatory | | 79 (15.2%) | 49 (18.7%) | 30 (11.7%) | | 79 (54.1%) | 0 (0.0%) | |
| Acutely ill: ambulatory | | 145 (27.9%) | 133 (50.8%) | 12 (4.7%) | | 24 (16.4%) | 121 (32.4%) | |
| Healthy looking | | 295 (56.8%) | 80 (30.5%) | 215 (83.7%) | | 43 (29.5%) | 252 (67.6%) | |
| **Infectious co-morbidities** | | | | | | | | |
| Malaria[1]    Confirmed | | 7 (7.8%) | 6 (8.8%) | 1 (4.5%) | | 7 (11.5%) | 0 (0.0%) | |
| Suspected | 90 | 44 (48.9%) | 28 (41.2%) | 16 (72.7%) | **0.003** | 15 (24.6%) | 29 (100.0%) | **<0.001** |
| Negative | | 39 (43.3%) | 34 (50.0%) | 5 (22.7%) | | 39 (63.9%) | 0 (0.0%) | |
| Tuberculosis[3] | 518 | 4 (0.8%) | 1 (0.4%) | 3 (1.2%) | 0.37 | 2 (1.4%) | 2 (0.5%) | 0.32 |
| HIV[3] | 291 | 5 (1.7%) | 4 (4.0%) | 1 (0.5%) | 0.05 | 2 (2.9%) | 3 (1.3%) | 0.33 |
| Any infectious co-morbidity | 296 | 16 (5.4%) | 11 (10.5%) | 5 (2.6%) | **0.004** | 11 (15.1%) | 5 (2.2%) | **<0.001** |
| **Chronic co-morbidities** | | | | | | | | |
| Diabetes[2] | 519 | 40 (7.7%) | 20 (7.6%) | 20 (7.8%) | 0.95 | 28 (19.2%) | 12 (3.2%) | **<0.001** |
| High blood pressure (>130/80) | 508 | 163 (32.1%) | 56 (22.0%) | 107 (42.1%) | **<0.001** | 48 (33.6%) | 115 (31.5%) | 0.65 |
| Chronic cardiac disease history[2] | 514 | 18 (3.5%) | 13 (5.0%) | 5 (2.0%) | 0.06 | 12 (8.5%) | 6 (1.6%) | **<0.001** |
| Chronic pulmonary disease[2] | 518 | 9 (1.7%) | 2 (0.8%) | 7 (2.7%) | 0.10 | 2 (1.4%) | 7 (1.9%) | >0.99 |
| Current smoker[2] | 515 | 21 (4.1%) | 4 (1.5%) | 17 (6.7%) | **0.003** | 3 (2.1%) | 18 (4.8%) | 0.16 |
| Hypertension[2] | 518 | 77 (14.9%) | 39 (14.9%) | 38 (14.8%) | 0.99 | 42 (29.0%) | 35 (9.4%) | **<0.001** |
| Any chronic co-morbidity | 519 | 229 (44.1%) | 84 (32.1%) | 145 (56.4%) | **<0.001** | 78 (53.4%) | 151 (40.5%) | **0.008** |
| ≥2 chronic co-morbidities | 519 | 80 (15.4%) | 37 (14.1%) | 43 (16.7%) | 0.41 | 43 (29.5%) | 37 (9.9%) | **<0.001** |
| **Nutritional status[3]** | 470 | | | | 0.79 | | | 0.02 |
| Obese | | 84 (17.9%) | 48 (19.4%) | 36 (16.1%) | | 23 (21.5%) | 61 (16.8%) | |
| Overweight | | 166 (35.3%) | 85 (34.4%) | 81 (36.3%) | | 32 (29.9%) | 134 (36.9%) | |
| Normal weight | | 203 (43.2%) | 106 (42.9%) | 97 (43.5%) | | 43 (40.2%) | 160 (44.1%) | |
| Underweight | | 17 (3.6%) | 8 (3.2%) | 9 (4.0%) | | 9 (8.4%) | 8 (2.2%) | |
| **Anemia Status[4]** | | | | | | | | |
| Anemic | 213 | 26 (12.2%) | 19 (9.6%) | 7 (46.7%) | **<0.001** | 15 (25.0%) | 11 (7.2%) | **<0.001** |

[1] RDTs were performed for inpatients suspected of having malaria by clinical staff; routine testing was not available. Suspected malaria refers to cases for whom no RDT was performed, who received anti-malarial medications taken prior to enrollment, and who reported chills and/or fever (measured or reported).

[2] Condition was self-reported by patient at enrollment.

[3] Obesity: in adults BMI >=30, in children up to 19 years old: BMI-for-age-z-score >3 SD.  Overweight: in adults BMI <30 and >=25, in children: BMI-for-age-z-score 2-2.99 SD. Underweight: in adults: BMI <18.5, in children <-2 SD. Children <5 (n=8) were excluded from this analysis, of them 0/7 with valid anthropometric measurements were malnourished by WHZ, and 2/7 were MAM by MUAC (>=11.5 cm & <12.5 cm).

[4] Children <12 years old: Hemoglobin < 11 g/dL, Children 12-15 years old: Hemoglobin < 12 g/dL, Non-pregnant women >=15 years old: Hemoglobin < 12 g/ dL, Pregnant women >=15 years old: Hemoglobin < 11 g/dL, Males >=15 years old: Hemoglobin <13 g/dL

15

**Table 3: Unadjusted and Adjusted Odds of Hospitalization by Select Patient Characteristics**

| | Unadjusted Odds | | | Adjusted Odds[1] | | |
|---|---|---|---|---|---|---|
| | Point Estimate | 95% CI | p-value | Point Estimate | 95% CI | p-value |
| **Demographic Characteristics** | | | | | | |
| Age (ref: age<45 years) | | | | | | |
|   Age 45-64 years | 2.24 | (1.45-3.47) | **<0.001** | 2.42 | (1.53-3.83) | **<0.001** |
|   Age 65+ years | 12.28 | (6.04-26.76) | | 12.16 | (5.67-26.09) | |
| Male sex (ref: female) | 0.80 | (0.53-1.19) | 0.27 | 0.93 | (0.59-1.46) | 0.76 |
| South Sudan (ref: DRC) | 0.55 | (0.38-0.82) | **0.003** | 0.77 | (0.45-1.33) | 0.35 |
| National (ref: non-nationals) | 2.90 | (1.67-5.05) | **<0.001** | 2.48 | (1.31-4.69) | **0.005** |
| **Primary Reason for Testing** | | | | | | |
| COVID-19 like symptoms (ref: other)[2] | 3.35 | (2.22-5.04) | **<0.001** | 2.59 | (1.62-4.16) | <0.001 |
| **Clinical Presentation at Enrollment** | | | | | | |
| Low oxygen level (<94%) | 8.90 | (5.34-14.85) | **<0.001** | 7.77 | (4.22-14.29) | **<0.001** |
| **Symptoms at Enrollment (self-reported)** | | | | | | |
| Symptomatic (ref: asymptomatic) | 4.19 | (2.36-7.46) | **<0.001** | 2.78 | (1.47-5.27) | **0.002** |
| Cough | 3.02 | (2.00-4.56) | **<0.001** | 2.27 | (1.43-3.62) | **<0.001** |
| Fatigue/malaise | 3.58 | (2.40-5.34) | **<0.001** | 2.80 | (1.77-4.41) | **<0.001** |
| Shortness of breath | 19.16 | (11-33.39) | **<0.001** | 21.37 | (10.91-41.87) | **<0.001** |
| Chest pain | 5.33 | (3.4-8.35) | **<0.001** | 4.48 | (2.71-7.43) | **<0.001** |
| Wheezing | 9.78 | (3.16-30.25) | **<0.001** | 8.34 | (2.42-28.67) | **<0.001** |
| Joint pain | 2.69 | (1.74-4.17) | **<0.001** | 2.08 | (1.25-3.46) | **0.005** |
| Loss of appetite | 2.34 | (0.89-6.2) | 0.07 | 1.52 | (0.52-4.42) | 0.44 |
| Runny Nose | 1.49 | (1.00-2.24) | 0.05 | 1.43 | (0.91-2.25) | 0.12 |
| Sore Throat | 2.22 | (1.45-3.39) | **<0.001** | 2.29 | (1.43-3.68) | **<0.001** |
| Headache | 1.72 | (1.17-2.53) | **0.006** | 1.36 | (0.88-2.12) | 0.17 |
| Nausea | 3.31 | (1.73-6.31) | **<0.001** | 2.88 | (1.42-5.85) | **0.003** |
| Abdominal pain | 1.84 | (1.06-3.21) | **0.032** | 1.73 | (0.95-3.17) | 0.07 |
| Diarrhea | 2.21 | (0.93-5.24) | 0.07 | 2.44 | (0.94-6.29) | 0.07 |
| Chills | 1.79 | (1.03-3.11) | **0.04** | 1.83 | (0.91-3.70) | 0.09 |
| **Exposure** | | | | | | |
| Visit to health care facility | 1.55 | (1.05-2.3) | **0.03** | 1.41 | (0.91-2.18) | 0.12 |
| Worked outside the home | 1.66 | (1.11-2.48) | **0.01** | 2.56 | (1.61-4.06) | **<0.001** |
| Health care worker | 0.49 | (0.22-1.07) | 0.07 | 0.46 | (0.20-1.06) | 0.07 |
| **Comorbidities** | | | | | | |
| Any infectious comorbidity | 7.74 | (2.59-23.1) | **<0.001** | 4.92 | (1.46-16.62) | **0.01** |
| Diabetes | 7.14 | (3.52-14.48) | **<0.001** | 5.08 | (2.28-11.32) | **<0.001** |
| Chronic cardiac disease | 5.63 | (2.07-15.31) | **<0.001** | 3.65 | (1.21-11.04) | **0.02** |
| Hypertension | 3.94 | (2.39-6.49) | **<0.001** | 2.65 | (1.45-4.85) | **0.002** |
| Chronic comorbidities (ref: none) [3] | | | | | | |
|   One chronic comorbidity | 1.00 | (0.63-1.6) | **<0.001** | 1.19 | (0.70-2.05) | **0.002** |
|   Two or more chronic comorbidities | 3.79 | (2.27-6.39) | | 3.11 | (1.62-5.96) | |
| **Nutrition** | | | | | | |
| Body mass index[4] | | | | | | |
|   Obesity (ref: normal weight) | 1.40 | (0.78-2.52) | **0.02** | 1.00 | (0.52-1.95) | **0.01** |
|   Overweight (ref: normal weight) | 0.89 | (0.53-1.48) | | 0.70 | (0.39-1.25) | |
|   Underweight (ref: normal weight) | 4.19 | (1.52-11.78) | | 5.04 | (1.63-15.57) | |
| Anemic[5] | 4.30 | (1.84-10.04) | **<0.001** | 10.69 | (3.32-34.41) | **<0.001** |

[1] Individual risk factor models adjusted for age, sex, country of enrollment and (non)national status (fixed effects) and facility (random effect)

[2] Included travel, close contact with a confirmed case, or other reason

16

[3] Self-reported history of diabetes, chronic cardiac disease, chronic pulmonary disease, hypertension, asthma, current smoking, or a blood pressure at enrollment of >130/80.

[4] Obesity: in adults BMI >=30, in children up to 19 years old: BMI-for-age-z-score >3 SD.  Overweight: in adults BMI <30 and >=25, in children: BMI-for-age-z-score 2-2.99 SD. Underweight: in adults: BMI <18.5, in children <-2 SD. Children <5 (n=8) were excluded from this analysis, of them 0/7 with valid anthropometric measurements were malnourished by WHZ, and 2/7 were MAM by MUAC (>=11.5 cm & <12.5 cm).

[5] Children <12 years old: Hemoglobin < 11 g/dL, Children 12-15 years old: Hemoglobin < 12 g/dL, Non-pregnant women >=15 years old: Hemoglobin < 12 g/ dL, Pregnant women >=15 years old: Hemoglobin < 11 g/dL, Males >=15 years old: Hemoglobin <13 g/dL

17

**Table 4: Unadjusted and Adjusted Odds of Mortality by Select Patient Characteristics**

| | Unadjusted Odds | | | Adjusted Odds[1] | | |
|---|---|---|---|---|---|---|
| | Point Estimate | 95% CI | p-value | Point Estimate | 95% CI | p-value |
| **Demographic Characteristics** | | | | | | |
| Age (ref: age<45 years) | | | | | | |
|   Age 45-64 years | 8.79 | (2.41-32.0) | **<0.001** | 11.42 | (3.06-3.06) | **<0.001** |
|   Age 65+ years | 37.35 | (11.02-171.55) | | 49.75 | (12.23-202.33) | |
| Male sex (ref: female) | 1.62 | (0.63-4.13) | 0.31 | 2.11 | (0.73-6.15) | 0.17 |
| South Sudan (ref: DRC) | 2.25 | (0.95-5.31) | **0.06** | 5.79 | (0.89-37.83) | 0.07 |
| National (ref: non-nationals) | 3.68 | (0.85-15.83) | **0.08** | 8.9 | (1.87-42.39) | **0.006** |
| **COVID-19 Testing** | | | | | | |
| COVID-19 symptoms (ref: other reason)[2] | 17.58 | (4.07-75.87) | **<0.001** | 13.44 | (2.83-63.76) | **0.001** |
| **Clinical Presentation at Enrollment** | | | | | | |
| Acutely ill: non-ambulatory[3] | 191.56 | (25.43-1443.3) | **<0.001** | 164.67 | (18.87-1437.13) | **<0.001** |
| Low oxygen level (<94%) | 41.13 | (11.98-141.16) | **<0.001** | 25.29 | (6.42-99.54) | **<0.001** |
| **Symptoms at Enrollment (self-reported)** | | | | | | |
| Symptomatic (ref: asymptomatic) | | | | | | |
| Cough | 5.08 | (1.72-15.02) | **0.003** | 3.33 | (1.03-10.79) | **0.05** |
| Fatigue/malaise | 7.04 | (2.6-19.08) | **<0.001** | 7.09 | (2.26-22.25) | **<0.001** |
| Shortness of breath | 66.32 | (15.31-287.34) | **<0.001** | 36.45 | (7.69-172.87) | **<0.001** |
| Chest pain | 11.21 | (4.55-27.62) | **<0.001** | 6.37 | (2.32-17.51) | **<0.001** |
| Loss of taste/smell | 2.45 | (1.02-5.87) | **0.05** | 1.59 | (0.56-4.54) | 0.39 |
| Wheezing | 12.68 | (4.3-37.42) | **<0.001** | 11.54 | (3.04-43.83) | **<0.001** |
| Joint pain | 2.16 | (0.93-5.02) | 0.08 | 1.10 | (0.42-2.90) | 0.84 |
| Loss of appetite | 7.05 | (2.12-23.47) | **0.001** | 5.17 | (1.13-23.69) | **0.04** |
| **Exposure** | | | | | | |
| Visit to health care facility | 2.77 | (1.22-6.29) | 0.02 | 2.08 | (0.78-5.55) | 0.14 |
| **Comorbidities** | | | | | | |
| Confirmed/suspect malaria (ref: negative) | 0.33 | (0.09-1.19) | 0.09 | 0.14 | (0.02-0.91) | **0.04** |
| History of diabetes | 12.60 | (5.26-30.2) | **<0.001** | 4.49 | (1.59-12.63) | **0.004** |
| History of hypertension | 7.26 | (3.17-16.61) | **<0.001** | 2.82 | (1.06-7.49) | **0.04** |
| High blood pressure (>130/80) | 2.85 | (1.27-6.43) | 0.01 | 1.66 | (0.64-4.32) | 0.30 |
| Num. of chronic comorbidities (ref: none)[4] | | | | | | |
|   One chronic comorbidity | 1.57 | (0.42-5.94) | **<0.001** | 0.80 | (0.19-3.32) | **0.005** |
|   Two or more chronic comorbidities | 14.25 | (5.36-44.87) | | 4.96 | (1.51-16.31) | |

[1] Individual risk factor models adjusted for age, sex, country of enrollment and (non)national status (fixed effects) and facility (random effect)

[2] Included travel, close contact with a confirmed case, or other reason

[3] General appearance at enrollment classified by clinical staff at enrollment

[4] Self-reported history of diabetes, chronic cardiac disease, chronic pulmonary disease, hypertension, asthma, current smoking, or a blood pressure at enrollment of >130/80.

18

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19

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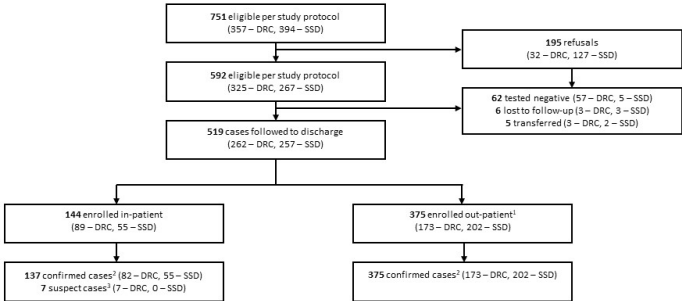21
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Figure 1. Study inclusion criteria flow chart
1 Of the 375 individuals enrolled outpatient, 2 individuals in South Sudan were subsequently admitted for in-patient care.
2 Cases were confirmed by real-time reverse transcription polymerase chain reaction (RT-PCR) (90% of confirmed cases) or antigen tests (10% of confirmed cases)
3 National case definitions were used to classify individuals as suspect cases. Of the suspect cases followed to discharge (n=7), 2 were never tested, 3 did not receive their test results, and 2 had specimens collected >3 days after enrollment.

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**Supplemental Table.** Characteristics of Health Facilities Enrolling Cases in this Study

| | Democratic Republic of the Congo | | | | South Sudan |
|---|---|---|---|---|---|
| **Hospital Location, Type and Study Enrollments** | | | | | |
| Location | Bukavu, South Kivu | Goma, North Kivu | Goma, North Kivu | Goma, North Kivu | Juba, Central Equatoria |
| Sector | Public | Public | Public | NGO operated | NGO operated |
| Study participants enrolled as inpatients | 25 | 0 | 42 | 22 | 55 |
| Study participants referred for home based care from facility catchment area | 64 | | 109[1] | | 202 |
| **Hospital Capacity** | | | | | |
| Doctors | 86 | 0 | 36 | 42 | 9 |
| Nurses | 168 | 7 | 92 | 86 | 33 |
| COVID care beds / Total beds[2] | 22/380 | NA | 20 / 220 | 28/220 | 82/82 |
| Clinical staff trained[3] | No | No | Yes | Yes | Yes |

[1] Study participants referred for home based care from throughout Goma, North Kivu. [2] The SSD facility was a COVID-19 only referral hospital and one of the Goma DRC facilities was an outpatient only facility; [3] Staff considered trained if they received information on COVID-19 case management and infection prevention and control (IPC) for COVID-19 prior to study initiation